PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#13
PS

In re Patent Application

Matzinger et al. Group: 1624

Serial No. 09/546,143, filed April 10, 2000 Examiner: Truong, T.

For: **ASYMMETRIC SYNTHESIS PROCESS**

**APPELLANT'S BRIEF (37 C.F.R. § 1.192)**

Nutley, New Jersey 07110
October 9, 2001

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

An original and two copies of this brief are submitted for the Board of Appeals. An additional copy is submitted for the purpose of charging our Deposit Account. This brief is in furtherance of the Notice of Appeal, mailed in this case on July 9, 2001 and received in the Patent Office on July 11, 2001. A petition for a one-month extension of time is believed to be necessary to make this brief timely filed. Please charge Deposit Account No. 08-2525 for the one-month extension fee of $110.00, the fee for filing a brief in support of an appeal of $320.00 and any other fee that is necessary for this filing.

## I REAL PARTY IN INTEREST (37 C.F.R. § 1.192(c)(1))

The real party in interest in this appeal is the assignee, Hoffmann-La Roche, Inc. of Nutley, New Jersey. This assignment was recorded on November 2, 1997 in parent application 08/832,253 on Reel 8788 in Frames 0472 and 0460.

## II RELATED APPEALS AND INTERFERENCES (37 C.F.R. § 1.192(c)(2))

There are no appeals or interferences which will directly affect, be directly affected by or have a bearing on the Board's decision in this appeal.

## III STATUS OF CLAIMS (37 C.F.R. § 1.192(c)(3))

### A. Total Number of Claims in Application

Claims in the application are: 10-27

### B. Status of All the Claims

1. Claims canceled: NONE
2. Claims withdrawn from consideration but not canceled: NONE
3. Claims pending: 10-27
4. Claims allowed: 10, 11 and 27
5. Claims objected to: 13, 16, 18, 20, 22 and 24
6. Claims rejected: 12, 14, 15, 17, 19, 21, 23 and 25

### C. Claims on Appeal

Claims 12-26 are on appeal.

## IV STATUS OF AMENDMENTS (37 C.F.R. § 1.192(c)(4))

No amendments were filed by Applicants subsequent to the final Office Action of April 9, 2001.

## V SUMMARY OF INVENTION (37 C.F.R. § 1.192(c)(5))

Applicants have discovered a new process for the synthesis of a class of azepine compounds known to have the pharmacologically useful property of inhibiting protein kinases. This application claims novel chemical intermediates useful in this synthesis. Since the pharmacologically useful end-products of this synthesis are limited to compounds which are a particular trans-enantiomer of the possible azepines (see Formula I on page 1 of the application), the synthesis is necessarily an asymmetric synthesis, with stereo-specific intermediates. Furthermore, since the novel intermediates are from steps in the synthesis process before de-protection of the amino group present in the final azepine compounds, all of the novel intermediates are bound by an amino-protecting group. The amino-protecting group serves the function of preventing undesired chemical modification of the amino group and will be removed from the final intermediate to produce the protein kinase-inhibiting azepine.

## VI ISSUES (37 C.F.R. § 1.192(c)(6))

i. Whether compound claims 12, 14, 15, 17, 19, 21, 23 and 25 are indefinite for reciting an "amino protecting group" substituent and are therefore properly rejected under 35 U.S.C. 112, second paragraph.

ii. Whether claims 17, 23 and 25, directed to cis-isomer compounds, are anticipated by prior art disclosures of trans-isomer compounds and are therefore properly rejected under 35 U.S.C. 102.

iii. Whether claim 17, directed to compounds in a specific stero-configuration in the absence of substantial amounts of other stereoisomers, is anticipated by a prior art disclosure of a mixture of stereoisomers, and is therefore properly rejected under 35 U.S.C. 102.

iv. Whether claims 25 and 26, directed to a particular compound with an amino-protecting group attached, are unpatentable under 35 U.S.C. 103 over a prior art disclosure of a broad encompassing genus.

## VII GROUPING OF CLAIMS (37 C.F.R. § 1.192(c)(7))

Claims 12, 14, 15, 17, 19, 21, 23 and 25 stand or fall together with regard to Issue (i), above. Claims 17, 23 and 25 stand or fall together with regard to Issue (ii), above. Claim 17 stands or falls alone with respect to Issue (iii), above. Claims 25 and 26 stand or fall together with regard to Issue (iv), above.

## VIII ARGUMENTS (37 C.F.R. § 1.192(c)(8))

**Issue (i): The rejection of claims 12, 14, 15, 17, 19, 21, 23 and 25 under 35 U.S.C. 112, first and second paragraph, as being indefinite or requiring undue experimentation for reciting an "amino protecting group, is improper and should not be upheld by the Board of Appeals.**

The final Office Action rejects claims 12, 14, 15, 17, 19, 21, 23 and 25 over their use of the term "amino-protecting group", which is alleged in the final Office Action to make these claims both indefinite and non-enabled.

The term "amino-protecting group", as used in the rejected claims, is well-known in the art to which this invention belongs, organic synthesis. The claimed "amino-protecting group" is a well known class of materials, all of whose members would be recognizable to one skilled in the art. As a demonstration of how well-known the term "amino-protecting group" is in the art, the undersigned agent searched the issued patent claims of the past 25 years on the USPTO website and found over 500 patents with the term "amino protecting group" in the claims. Applicants have also previously submitted to the Examiner a copy of the table of contents for Chapter 7, "Protection for the Amino Group" from Protective Groups in Organic Synthesis by Theodora W. Green, published in 1981 by John Wiley & Sons, Inc. As shown in the table of contents for that particular chapter, "amino protecting groups" are well-known and exemplified by many members, all of which are within the skill of the art of organic synthesis. As shown by such wide-spread and text-book use, this term is well-known in the art.

Terms that define a well-known class of materials, the members of which would be ascertainable to one skilled in the art, comply with 35 U.S.C. 112, first and second paragraph. In this manner, terms such as "water soluble hydrolyzable carbohydrate", *In re Skoll*, 187 USPQ 481 (CCPA 1975); "organic and inorganic acids", *In re Skoll*, supra; "inorganic salts", *In re Fuetterer*, 138 USPQ 217 (CCPA 1963); "polymerizable materials", *In re Bowen*, 181 USPQ 48 (CCPA 1974); and "organic radical", *In re Robins*, 166 USPQ 552 (CCPA 1970) have been held to comply with 35 U.S.C. 112, first and second paragraph.

The fact that the instant term "amino-protecting group" covers many different substituents is not a sufficient basis for a rejection under 35 U.S.C. 112. As stated by the CCPA in holding that the term "organic and inorganic acids" is not indefinite under 35 USC 112:

> We first consider the expression 'organic and inorganic acids', which is said to be indefinite and of uncertain scope. We cannot agree. Although there are undoubtably a large number of acids which come within the scope of 'organic and inorganic acids', the expression is not for that reason indefinite. We see no reason to believe that the public would be confused as to what subject matter is circumscribed by applicant's claim. *In re Skoll*, supra at 482.

The "amino-protecting group" term improperly rejected in this application is no less rigorously defined than the "organic and inorganic acids" upheld by the CCPA in *Skoll*. As noted above, Applicants' "amino-protecting group" defines a well known class of substituents used in chemical synthesis, all of whose members would be recognizable to one skilled in the art.

The definition of the $R^4$ groups of the claims by their particular function, being amino-protecting groups, and not by particular chemical structures also fails to make the term or the claims indefinite under 35 U.S.C. 112. In reversing a 35 U.S.C. 112 rejection of a claim term to "an inorganic salt that is capable of holding a mixture of said carbohydrate and protein in colloidal suspension in water", the CCPA specifically approved use of such functional limitations:

> It is true that appellant's inorganic salt *is* defined in terms of "what it does" rather than "what it is." We note, however, that the Supreme Court, in a seldom quoted passage in the Wabash case, stated, 37 USPQ at 469:
>
> > A limited use of terms of effect or result, which accurately define the essential qualities of a product to one skilled in the art, may in some instances be permissible and even desirable ...
>
> Appellant in the instant case has made just such a use of terms of result to define an essential quality of his inorganic salts. (Emphasis in original) *In re Fuetterer*, supra at 222.

Regarding the instant application in particular, Applicant's note that there is no effective substitute for functional language in claiming the compounds of this application. All of the compounds claimed are *intermediates*, useful for the synthesis of a particular endproduct, which has valuable pharmacological properties. At some point during the conversion of the instantly claimed intermediates into that pharmaceutical, the "amino-protecting groups" will be removed to expose the amino group present in that pharmaceutical. Therefore, the exact identity of the "amino-protecting group" is unimportant, but its function (binding the amino group early during the synthesis of the medicine, preventing modification of the amino group during various stages of chemical synthesis and releasing from the amino group at the end of the synthesis to expose the amino group) is critical. Accordingly, since the functionally defined genus "amino-protecting group" is well-known and understood in the art of organic synthesis, Applicants have properly used that term to describe that critical function in the instantly claimed compounds.

For all of the above reasons, the instant rejection of claims 12, 14, 15, 17, 19, 21, 23 and 25 under 35 U.S.C. 112 for containing the term "amino-protecting group" is improper and should be withdrawn. "Amino-protecting group" defines a well-known and understood class of chemical groups, all of whose members would be recognizable to one skilled in the art; the instant term, claiming groups with the functional limitation that they are amino protecting, accurately defines the essential qualities of those particular

groups to one of skill in the art; and the simple fact that the term is broad does not make it indefinite.

Regarding the allegation in the final Office Action that "amino-protecting group" is non-enabled in the instant claims because only one species is disclosed in the specification, Applicants again refer to the text-book chapter cited above. This text, published in 1981, is just one example of a whole host of knowledge about the identity and use of amino-protecting groups that was known to the skilled organic chemist when this application was filed. It is not necessary for an Applicant to teach in the specification what is well-known in the art, and amino-protecting groups are well-known in the art. Therefore, the applicant is not required to provide the specification with *any* examples of amino-protecting groups, much less the exhaustive listing required by implication in the final Office Action.

**Issue (ii): Claims 17, 23 and 25, directed to cis-isomer compounds, are not anticipated by prior art disclosures of trans-isomer compounds and their rejection under 35 U.S.C. 102 is improper and should not be upheld by the Board of Appeals.**

The rejection of claim 23 under 35 U.S.C. 102(a) over Lampe et al. or under 35 U.S.C. 102(b) over Adams et al. is improper and should not be upheld by the Board of Appeals. Applicants respectfully refer the Board of Appeals to Formula X of claim 23, which clearly requires the hydroxyl and amino groups to be in a cis formation to each other (both groups are on the same side of the ring structure). The compounds cited by the Examiner as anticipating claim 23 (compound 25 of Lampe et al. and compound 20 of Adams et al.) both clearly show a trans formation for the hydroxyl and amino groups, meaning that each group is on a different side of the ring structure. The trans-configuration taught by Lampe et al. and Adams et al. does not encompass the cis compounds of claim 23. Simply put, the prior art teaches structurally different compounds than those instantly claimed in claim 23. The prior art cited fails to teach a limitation of claim 23, namely that the hydroxyl and amino groups are in a cis formation.

Accordingly, an anticipation rejection under 35 U.S.C. 102(a) or (b), which requires that "the invention ... was patented or described in a printed publication" is improper.

The rejection of claim 25 under 35 U.S.C. 102(a) over Adams et al. is improper and should not be upheld by the Board of Appeals. Again, the instant claim specifies a cis arrangement between the hydroxyl group and the $NHR^1$ group, whereas the compound cited by the Examiner, compound 21 of Adams et al., has a trans arrangement. The trans-configuration taught by Adams et al. does not encompass the cis compounds of claim 25. Furthermore, Adams et al. fails to teach a limitation of claim 25, namely that they hydroxyl group and the $NHR^1$ group are in the cis formation.

The rejection of claim 25 under 35 U.S.C. 102(a) over the disclosure of compounds B1-23 of Barbier et al. is improper and should not be upheld by the Board of Appeals. The exemplified compounds of Barbier et al. are all in the trans formation (3R, 4R). Again, the teaching of the trans formation does not anticipate the instantly claimed, structurally distinct, cis formation.

The rejection of claim 17 under 35 U.S.C. 102(a) over the disclosure of compound 13 of Krogsgaard-Larsen et al. is improper and should not be upheld by the Board of Appeals. Compound 13 of Krogsgaard-Larsen et al. has a trans configuration between the hydroxyl and ester groups. Since compound 13 of Krogsgaard-Larsen et al. does not encompass the compounds of claim 17, which have a cis configuration between the hydroxyl and ester groups, compound 13 fails to anticipate claim 17.

Applicants note that the Advisory Action, in point 1 on page 2, makes a new argument that the instantly claimed "*cis* configuration is **inherently embraced** by the [prior art disclosed] *trans* configuration because if one configuration exists, the other also exists even though in small quantity" (emphasis in original). It is simply not true that a cis-configuration molecule inherently embraces the trans-configuration; the two molecules are structurally distinct. To the extent that the Advisory Action appears to make an argument based on conjectured cis-configuration contaminants of the trans-

configuration compounds disclosed in the prior art, Applicants respectfully submit that the cited prior art fails to recognize or suggest these conjectured contaminants, and the instant prosecution history fails to provide any prior art support for the Examiner's conjecture. Even were the Examiner's conjecture both true and documentable, an accidental contaminant unrecognized by the prior art does not place the contaminant sufficiently within the public domain to support an anticipation rejection. For instance, even if the cited trans-configuration prior art did inherently contain minor amounts of a cis-contaminant, the instant claims would not be anticipated, because the prior art does not provide an enabling disclosure of how to make the instantly claimed cis-configuration compound in anything other than trace amounts. Applicants also submit that the Advisory Action's conjectured contaminant reasoning cannot be applied to claim 17, because that claim includes a limitation that the claimed enantiomer is "in the absence of substantial amounts of other enantiomers of the compound."

**Issue (iii): Claim 17, directed to compounds in a specific stero-configuration in the absence of substantial amounts of other stereoisomers, is not anticipated by a prior art disclosure of a mixture of stereoisomers, and its rejection under 35 U.S.C. 102 is improper and should not be upheld by the Board of Appeals.**

The rejection of claim 17 under 35 U.S.C. 102(a) over the disclosure of compound 12 of Krogsgaard-Larsen et al. is improper and should not be upheld by the Board of Appeals. Compound 12 of Krogsgaard-Larsen et al. is a racemic mixture of cis-hydroxy esters, including *both* a cis-hydroxy ester enantiomer according to claim 17 (note that both hydroxy and ester groups are pointed down from the ring structure) *and* another cis-hydroxy ester enantiomer which is depicted as compound 12 in Scheme 2 of Krogsgaard-Larsen et al. (note that both hydroxy and ester groups are pointed up from the ring structure). These two enantiomers are distinct, and Krogsgaard-Larsen discloses a mixture of them, as shown by the notation "(±)12" used in Scheme 2 on page 328 of Krogsgaard-Larsen et al. However, claim 17 excludes the racemic mixture disclosed as compound 12 in Krogsgaard-Larsen et al., because claim 17 defines the hydroxy and ester groups as being pointed down from the ring structure and has a limitation requiring the absence of substantial amounts of enantiomers of the claimed compounds (such as the

hydroxy and ester groups pointed up from the rings structure). This limitation is not taught or suggested by Krogsgaard-Larsen et al. Furthermore, since Krogsgaard-Larsen et al. fails to teach or suggest any motivation or method for separating the racemic mixture into substantially pure isomers, Krogsgaard-Larsen et al. fails to enable or make obvious the enatiomerically pure compounds of claim 17.

**Issue (iv): Claims 25 and 26, directed to a particular compound with an amino-protecting group attached, are patentable under 35 U.S.C. 103 over a prior art disclosure of a broad encompassing genus, because the prior art fails to place the claimed compounds in the public domain.**

The rejection of claims 25 and 26 under 35 U.S.C. 103 over Barbier et al. is improper and should not be upheld by the Board of Appeals. Barbier et al. fails to place the compounds of instant claim 25 in the public domain because 1) the generic chemical formula III of Barbier et al. fails to disclose the instantly claimed compounds and/or 2) Barbier fails to provide an enabling disclosure of the instantly claimed compounds.

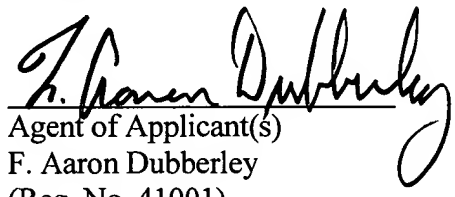
As the final Office Action correctly pointed out, a "generic chemical formula will anticipate a claimed species covered by the formula when the species can be 'at once envisioned' from the formula." Here, the instantly species of claim 25 cannot be "at once envisioned" from the generic chemical formula III of Barbier et al. Applicants respectfully submit that formula III of Barbier et al., as depicted in column 9, lines 3-10, encompasses millions of compounds. Note that A in formula III is defined in column 1, lines 20-30, and can encompass any of at least 6 different ring structures with each and every ring atom being optionally substituted by lower-alkyl, lower-alkoxy and hydroxy groups, with some ring atoms having additional possible substituents. Therefore, each position of each ring structure has at least 12 possible substituents, or $12^5 \cong 250{,}000$ possibilities per ring structure. Once all six possible ring structures are considered, there are at least 1.5 million possibilities. Compound these 1.5 million possibilities for A with the two possibilities for Y, the three for the central ring structure of Barbier's formula III and various particular enantiomers of each of those compounds, and the number of possibilities is well over 10 million. Applicants respectfully submit that the Examiner

has yet to present any reason why the instantly claimed specific enantiomers can be "at once envisioned" from such a large group of possibilities. Accordingly, this rejection is improper and must fail.

The rejection of claims 25 and 26 under 35 U.S.C. 103 over Barbier et al. is also improper because Barbier fails to provide an enabling disclosure for the instantly claimed compounds (see MPEP 2121.02, which exemplifies the current state of patent law on this subject). The compounds of claims 25 and 26 are specific cis stereoisomers. These specific stereoisomers are necessary to obtain the object of the invention, the asymmetric synthesis of a biologically useful class of stereoisomers. Barbier et al. fails to teach or suggest to one of skill in the art how to make any cis isomers. Applicants respectfully note that *all* of the examples taught by Barbier (B1-23) are trans isomers. The disclosure of Barbier et al. leaves one of skill in the art with no direction as to how to make the cis compounds of claims 25 and 26. Accordingly, this rejection is improper and must fail.

Reversal of all rejections of the claims on appeal is requested.

Respectfully submitted,



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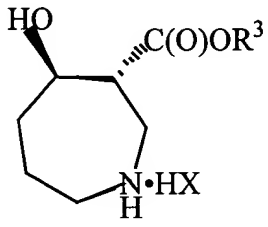
## IX APPENDIX OF CLAIMS (37 C.F.R. § 1.192(c)(9))

10. (twice amended) A compound selected from the group consisting of compounds of the formula

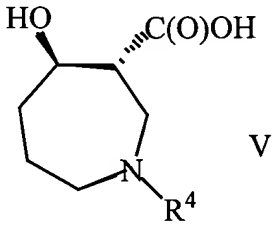



IV,

wherein $R^3$ is lower alkyl and HX is an acid.

11. (amended) The compound of claim 10, wherein the compound is ethyl (3R,4R)-4-hydroxy-azepan-carboxylate hydrochloride.

12. (twice amended) A compound selected from the group consisting of compounds of the formula

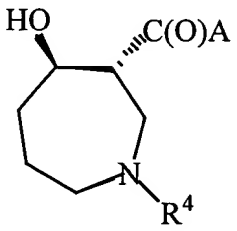



V

wherein $R^4$ is an amino-protecting group.

13. (amended) The compound of claim 12, wherein the compound is (3R,4R)-4-Hydroxy-azepan-1,3-dicarboxylic acid 1-tert.-butyl ester.

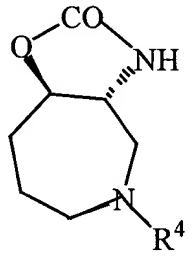
14. (twice amended) A compound selected from the group consisting of compounds of the formula




Va

wherein A is azido or amino and $R^4$ is an amino-protecting group.

15. (twice amended) A compound selected from the group consisting of compounds of the formula

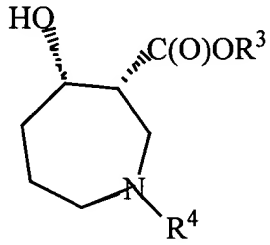



VI,

wherein $R^4$ is an amino-protecting group.

16. (amended) The compound of claim 15, wherein the compound is (3aR,8aR)-5-tert-Butoxycarbonyl-2-oxo-octahydro-oxazolo(4,b-c)azepine.

17. (twice amended) A compound selected from the group consisting of compounds of the formula

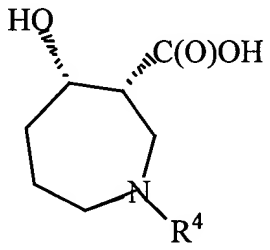



VIII,

wherein $R^3$ is lower alkyl and $R^4$ is an amino-protecting group,
in the absence of substantial amounts of other enantiomers of the compound.

18. (amended) The compound of claim 17, wherein the compound is ethyl (3R,4S)-1-(tert-butoxycarbonyl)-4-hydroxy-azepan-3-carboxylate.

19. (twice amended) A compound selected from the group consisting of compounds of the formula

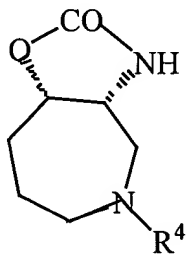



VIIIa,

wherein $R^4$ is an amino-protecting group.

20. (amended) The compound of claim 19, wherein the compound is (3R,4S)-4-Hydroxy-azepan-1,3-dicarboxylic acid 1-tert-butyl ester.

21. (twice amended) A compound selected from the group consisting of compounds of the formula

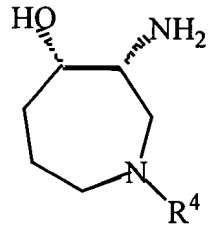



IX,

wherein $R^4$ is an amino-protecting group.

22. (amended) The compound of claim 21, wherein the compound is tert.Butyl (3aR,8aS)-2-oxo-octahydro-oxazolo(4,b-c)azepine-5-carboxylate.

23. (twice amended) A compound selected from the group consisting of compounds of the formula

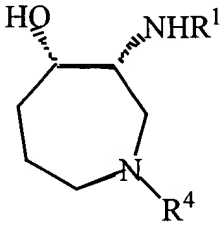



X,

wherein $R^4$ is an amino-protecting group.

24. (amended) The compound of claim 23, wherein the compound is tert-Butyl (3R,4S)-3-amino-4-hydroxy-azepan-1-carboxylate.

25. (twice amended) A compound selected from the group consisting of compounds of the formula




XI,

wherein $R^1$ is an acyl residue of an aromatic carboxylic acid and $R^4$ is an amino-protecting group.

26. (amended) The compound of claim 25, wherein the compound is tert-Butyl (3R,4S)-3-(4-tert-butoxy-benzoylamino)-4-hydroxy-azepan-1-carboxylate.

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# Inhibitors of GABA Uptake. Syntheses and $^1$H NMR Spectroscopic Investigations of Guvacine, (3*RS*,4*SR*)-4-Hydroxypiperidine-3-carboxylic Acid, and Related Compounds

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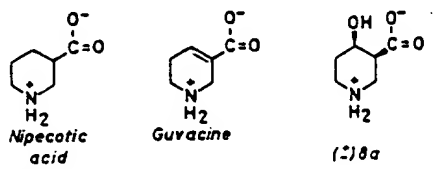
The syntheses of (3*RS*,4*SR*)-4-hydroxypiperidine-3-carboxylic acid (*8a*) and guvacine (1,2,5,6-tetrahydropyridine-3-carboxylic acid) hydrobromide (*9a*), both potent inhibitors of γ-aminobutyric acid (GABA) uptake, are described. Furthermore (3*RS*,4*SR*,5*SR*)- and (3*RS*,4*SR*,5*RS*)-4-hydroxy-5-methylpiperidine-3-carboxylic acids (*8c*) and (*8d*) and the guvacine analogues (*RS*)-5-methyl-1,2,5,6-tetrahydropyridine-3-carboxylic acid (*10*) and 2,5,6,7-tetrahydro-1*H*-azepine-3-carboxylic acid and (1*R*,5*S*)-(−)-2-nortropene-2-carboxylic acid hydrobromides (*14*) and (*18*) have been synthesized. The compounds *8a,c,d*, *9a*, *10*, and *14* were prepared *via* catalytic hydrogenation of cyclic β-oxoesters and appropriate acid treatments of the intermediate β-hydroxy esters. Demethylation of ecgonine (*16*) followed by acid catalyzed hydrolysis and elimination reactions gave *18*. (*RS*)-Perhydroazepine-3-carboxylic acid and (1*R*,2*R*,5*R*)-(+)-nortropane-2-carboxylic acid hydrobromides (*15*) and (*19*) were obtained by catalytic hydrogenation of *14* and *18*, respectively. The relative stereochemistry of *6a,c,d*, *12*, *13*, and *19* was established by 270 MHz $^1$H NMR spectroscopy. The relationship between structure and potency as inhibitors of GABA uptake of *8a,c,d*, *9a*, *10*, *14*, *15*, *18*, and *19* is discussed.

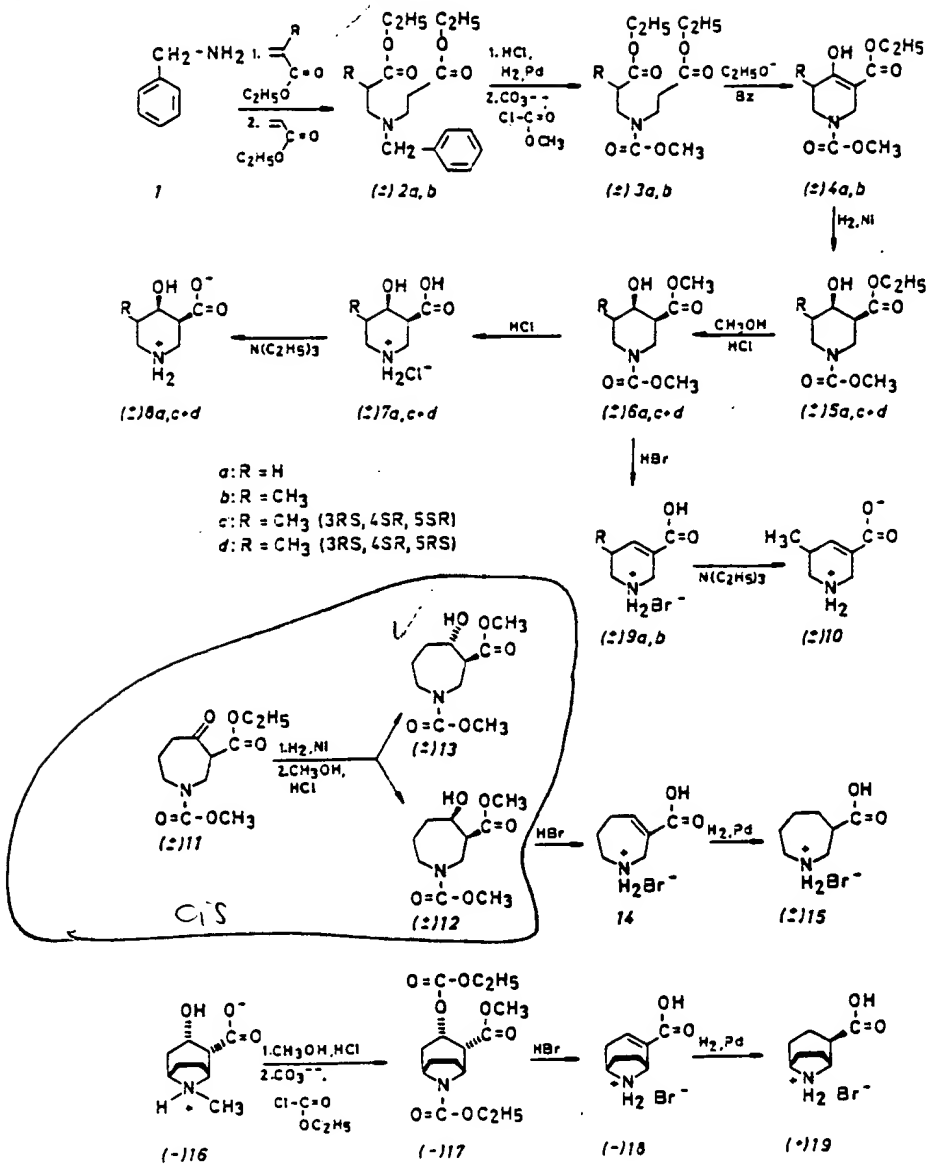



*Scheme 1.*

Nipecotic acid (piperidine-3-carboxylic acid),[1–3] guvacine (1,2,5,6-tetrahydropyridine-3-carboxylic acid),[4] and (3*RS*,4*SR*)-4-hydroxypiperidine-3-carboxylic acid (*8a*)[5] (Scheme 1) are potent substrate-competitive inhibitors of the neuronal γ-aminobutyric acid (GABA) uptake process. The concentrations of (*R*)-(−)-nipecotic acid, guvacine, and compound *8a* required for 50 % inhibition of GABA uptake ($IC_{50}$ values) are 5 μM,[3] 8 μM,[4] and 12 μM,[5] respectively. These compounds seem to combine with the GABA transport carrier and penetrate the tissue.[2–4] Such compounds have pharmacological interest and may be useful tools for the study of the GABA transport carrier. However, molecular manipulations of these amino acids result in compounds with considerably reduced potency as inhibitors of GABA uptake, the $IC_{50}$ values of *8c*, *8d*, *10*, and *15* being 260,[6] 349,[5] 547,[5] and 502 μM,[6] respectively. Compound *14*[6] and the conformationally rigid amino acids *18*[6] and *19*[6] are almost inactive. These findings demonstrate a pronounced substrate specificity of the GABA transport carrier.

This paper describes the syntheses of *8a*, its 5-methyl derivatives *8c* and *8d*, and the guvacine and nipecotic acid analoques *10*, *14*, *18*, *15*, and *19*. A convenient method for the preparation of guvacine hydrobromide (*9a*) has been developed. Guvacine hydrochloride has previously been synthesized on a very small scale.[7,8]

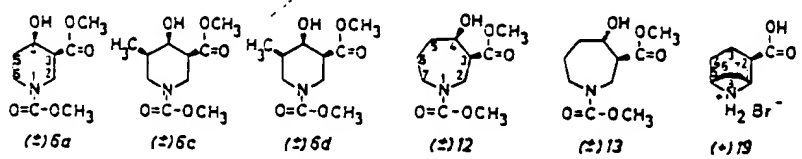
The β-oxoester *4b* was the only detectable product after Dieckmann cyclization of the unsymmetrical diester *3b* (Scheme 2). High pressure hydrogenation of *4a,b* gave the 3,4-*cis*-4-hydroxynipecotic acid derivatives *5a* and



*Scheme 2.*

a separable mixture of *5c* and *5d*, respectively. The ethyl esters *5a,c,d* were transformed into the corresponding methyl esters in order to facilitate the analysis of the 270 MHz $^1$H NMR spectra. Reduction of the *β*-oxoester *11*, however, gave a separable mixture of the *cis*- and *trans*-*β*-hydroxy esters *12* and *13* (Scheme 2). Appropriate treatmetnts of *6a,c,d* with hydrochloric acid gave the hydroxy amino acid chlorides *7a,c,d*, whereas the compounds *9a,b* were synthesized by prolonged treatments of *6a* and *6c* with hydrobromic acid. *N*-Demethylation of the methyl ester of ecgonine [(1*R*,2*R*, 3*S*,5*S*)-(−)-3-hydroxytropane-2-carboxylic acid]

*Table 1.* Some chemical shifts ($\delta$) and coupling constants (Hz) from the 270 MHz $^1$H NMR spectra of *6a,c,d*, *12*, *13*, and *19*.[a]



(±)6a (±)6c (±)6d (±)12 (±)13 (+)19

| | (±)6a | (±)6c | (±)6d | (±)12 | (±)13 | (+)19 |
|---|---|---|---|---|---|---|
| $\delta_{1e}$ | – | – | – | – | – | 4.15 |
| $\delta_{2a}$ | 3.43 | 3.19 | *ca.* 3.7 | 3.38 | 3.17, 3.22 | 2.88 |
| $\delta_{2e}$ | 4.05 | 4.23 | *ca.* 3.7 | 3.92, 4.07 | 3.79, 3.96 | |
| $\delta_{3a}$ | 2.64 | 2.58 | 2.81 | 2.71, 2.78 | 2.60, 2.66 | |
| $\delta_{4a}$ | – | – | – | – | 3.91 | |
| $\delta_{4e}$ | 4.32 | 4.17 | 3.79 | 4.32 | – | |
| $\delta_{5a}$ | 1.66 | 1.68 | – | 1.53 | 1.62 | |
| $\delta_{5e}$ | 1.94 | – | 1.98 | 2.06 | 1.90 | 3.93 |
| $\delta_{6a}$ | 3.30 | 2.32 | 3.23 | 1.69 | 1.62 | |
| $\delta_{6e}$ | 3.79 | 3.80 | 3.59 | 2.06 | 2.00 | |
| $\delta_{7a}$ | – | – | – | 3.20, 3.25 | 3.32 | |
| $\delta_{7e}$ | – | – | – | 3.64 | 3.56 | |
| $\delta$C–COOC*H*$_3$ | 3.68 | 3.69 | 3.69 | 3.71, 3.72 | 3.69 | |
| $\delta$N–COOC*H*$_3$ | 3.71 | 3.73 | 3.72 | 3.74, 3.75 | 3.75 | |
| $\delta$C–C*H*$_3$ | – | 0.99 | 0.98 | – | – | |
| $J_{1e2a}$ | – | – | – | – | – | 2.2 |
| $J_{2a2e}$ | −13.2 | −13.0 | | −14.5 | −14.8 | |
| $J_{2a3a}$ | 10.7 | 12.0 | 10.0[b] | 10.2 | 9.0 | |
| $J_{2e3a}$ | 4.5 | 2.0 | 2.6[b] | 3.0 | 3.75 | |
| $J_{3a4e}$ | 2.5 | 4.4 | 3.4 | 3.0 | – | |
| $J_{3a4a}$ | – | – | – | – | 9.0 | |
| $J_{4a5e}$ | – | – | – | – | 2 | |
| $J_{4a5a}$ | – | – | – | – | 9 | |
| $J_{4e5a}$ | 3.0 | *ca.* 4 | – | | – | |
| $J_{4e5e}$ | 4.4 | – | 5.3 | | – | |
| $J_{5a5e}$ | −13.6 | – | – | | | |
| $J_{5a6a}$ | 11.7 | 12.0 | | | | |
| $J_{5a6e}$ | 4.8 | *ca.* 2 | | | | |
| $J_{5e6a}$ | 3.2 | – | 5.4 | | | |
| $J_{5e6e}$ | 3.4 | – | 3.4 | | | |
| $J_{6a6e}$ | −13.4 | −13.0 | −13.6 | | | |
| $J_{7a7e}$ | – | – | – | −14 | | |

[a] The spectra of *6a,c,d*, *12*, and *13* were recorded in $CDCl_3$ and that of *19* in $D_2O$ solutions. [b] Only the sum of $J_{2a3a}$ and $J_{2e3a}$ is precisely determined.

(*16*) by a modified von Braun procedure[9] followed by acid hydrolysis and dehydration of the intermediate *17* (Scheme 2) gave the rigid guvacine analogue *18*. Hydrogenation of *18* proceeded stereospecifically, *19* being the only detectable product.

The structure elucidation of the new products *2b* – *4b*, *5* – *10*, *12* – *15*, and *17* – *19* were based on elemental analyses, IR and $^1$H NMR spectroscopy, in the cases of *9a,b*, *10*, *14*, and *18* supported by UV spectroscopy. In tetrachloromethane solution the β-oxoester *4b* (Scheme 2) exists in the enol-form as established by $^1$H NMR spectroscopy. The relative configurations of *5* – *8*, *12*, *13*, and *19* were established by analysis of the 270 MHz $^1$H NMR spectra of the methyl esters *6a,c,d*, *12*, and *13* and compound *19*, respectively.

In simple piperidine derivatives the equatorial proton on C(2) is found downfield from its axial counterpart.[10] The coupling constants between the C(3) proton and the two C(2) protons are typical for equatorial-axial and axial-axial configurations of these protons in *6a*. This is consistent with a predominantly equatorial orientation of the C(3) methoxycarbonyl group (Table 1). Furthermore the coupling constant for the C(3) and C(4) protons unequivocally indicates axial-equatorial orientation of the protons concerned and therefore a 3,4-*cis* configuration of *6a*. An analysis of the mutual coupling constants for the C(4) and C(5) protons supports this assignment. The vicinal coupling constants used in this assignment are in general agreement with those found in most 6-membered rings.[11] The geminal coupling constants found parallel data previously found in other piperidines.[12] The coupling patterns of the C(2), C(3), and C(4) protons in *6c* are very similar to those of the corresponding system in *6a* establishing equatorial and axial positions of the substituents at C(3) and C(4), respectively. The coupling constants for the C(5) proton indicate an equatorial orientation of the C(5) methyl group. These findings together are in agreement with the depicted relative configuration of *6c*. In *6d* the mutual coupling constants for the C(6) and C(5) protons indicate an axial orientation of the C(5) methyl group. A further analysis of the C(5), C(4), and C(3) proton coupling patterns reveals axial and equatorial orientations of the hydroxy and C(3) methoxycarbonyl groups, respectively.

In previous studies of piperidines[10] it has been suggested that the chemical shift difference between axial and equatorial protons on C(2) and C(6) ($\Delta\delta$) would indicate the extent to which the nitrogen lone pair influences the two protons. The differences $\Delta\delta(H_{2a},H_{2e})$ and $\Delta\delta(H_{6a},H_{6e})$ found in *6a* would be consistent with the dominating contribution from the equatorial-axial orientation of the C(3) and C(4) substituents of *6a*. The $\Delta\delta$ values found for *6c* are larger, indicating an increased fixation in an equatorial-axial-equatorial arrangement of the C(3), C(4), and C(5) substituents. This tendency is reflected in the values of the axial-axial coupling constants, where $J_{aaa} = 12.0$ Hz would be consistent with an almost locked conformation. In *6d* the spectrum is quite different. The two protons at C(2) are almost coinciding in chemical shift at a value of *ca.* 3.7 ppm, the lack of accuracy arising from the near coincidence of the signal with those of the methoxy groups. The chemical shift difference between the two protons at C(2) can be judged from the triplet structure of the C(3) proton in the ABX pattern formed by the three protons at C(2) and C(3). The vanishingly small chemical shift difference on C(2) and the reduced chemical shift difference on C(6) as well as the smaller value of $J_{aaa}$ in *6d* (10.0 Hz) all point to a conformational equilibrium where equatorial-axial-axial orientations of the C(3), C(4), and C(5) substituents represent the preferred but not the exclusive conformation.

The 270 MHz $^1$H NMR spectra of *12* and *13* were analysed as far as the complexity of the spectra permitted. Interpretation of the spectra, recorded at 293 K, was complicated by the fact that both molecules gave rise to two sets of signals due to hindered rotation of the urethane group. This is reflected in dual values for several chemical shifts while the coupling constants determined in both conformers were identical. The coupling constants clearly indicate that the arrangement of the substituents in position 3 and 4 are equatorial-axial in *12* and equatorial-equatorial in *13*. The observed values for chemical shifts and coupling constants are in general agreement with the data given for *6a*. In the spectrum of *19* a merging and very complex pattern of signals from the C(3), C(4), C(6), and C(7) protons is observed. It is not possible to establish the orientation of the carboxyl group of *19* on the basis of the coupling constant for the equatorial C(1) proton and the proton on C(2). However, the total width of the pattern originating in the C(2) proton reveals the existence of an axial-axial coupling between this proton and the axially oriented C(3) proton thus indicating an equatorial orientation of the carboxyl group.

## EXPERIMENTAL

Unless otherwise stated, the determination of melting points and elemental analyses and the recording of IR, UV, and 60 MHz $^1$H NMR spectra were accomplished as described in a previous paper.[13] $^1$H NMR spectra of compounds dissolved in $D_2O$ were recorded by using sodium 3-(trimethylsilyl)propanesulfonate as an in-

ternal standard. The 270 MHz $^1$H NMR spectra were obtained on a Bruker HX 270 S instrument operating at 293 and 303 K. Fourier transform method was used to obtain the spectra with a spectral width of 1500 Hz using 32 K data points. The detection was quadrature detection. Homodecoupling was used to verify the interpretations of the spectra and provide starting parameters for the analyses of the spectra. Nitrogen decoupling was possible using a Bruker probehead equipped with an additional nitrogen decoupling coil. The frequency was derived from a Bruker synthesizer model BS 100 and fed to the amplifier of the decoupling channel through a band pass filter before entering the probe. The decoupling power was 5 watt. The decoupling frequency used was 19 506 582 Hz. The proton spectra were analyzed using the program SIMEQ and a Varian 620/i computer. Due to the large chemical shift differences at 270 MHz, it is permissible to subdivide the total spin system into several subsystems containing typically 3 to 6 nuclei. After the initial assignment the spectra were iterated to a best fit using the ITRCAL program on a Nicolet 1180 computer with 80 K memory. Optical rotations were measured on a Perkin-Elmer polarimeter model 141. Thin-layer chromatography (TLC) and column chromatography (CC) were accomplished by using silica gel $F_{254}$ plates (Merck) and silica gel (Woelm 0.063 – 0.1 mm), respectively. Columns were developed by stepwise gradient elution. The $pK_A$ values were determined as described in a previous paper.[14]

*(RS)-Ethyl N-benzyl-N-(2-ethoxycarbonylethyl)-2-methyl-3-aminopropionate* (2b). To a solution of *1* (107 g; 1 mol) in ethanol (200 ml) was added ethyl methacrylate (137 g; 1.2 mol). The mixture was refluxed for 24 h, the solvent removed *in vacuo*, and the residue distilled to give (*RS*)-ethyl *N*-benzyl-2-methyl-3-aminopropionate (149.9 g; 68 %), b.p. 131 – 133 °C/80 Pa. Anal. $C_{12}H_{19}NO_2$: C, H, N. IR (film): 3330 (w), 3030 (w), 2970 – 2820 (m), 1725 (s), 1495 (m), 1450(m) cm$^{-1}$. $^1$H NMR (60 MHz, $CCl_4$): $\delta$ 7.17 (5 H, s), 3.98 (2 H, q, *J* 7 Hz), 3.63 (2 H, s), 3.0 – 2.1 (3 H, m), 1.42 (1 H, s), 1.33 – 0.97 (6 H, m).

A solution of (*RS*)-ethyl *N*-benzyl-2-methyl-3-aminopropionate (142.3 g; 0.65 mol) and ethyl acrylate (83.9 g; 0.84 mol) in ethanol (150 ml) was refluxed for 4 days. The solvent was removed *in vacuo*, and distillation of the residue gave *2b* (164.8 g; 79 %), b.p. 165 – 167 °C/47 Pa. Anal. $C_{18}H_{27}NO_4$: C, H, N. IR (film): 3030 (w), 2980 (m), 2810 (m), 1730 (s), 1495 (w), 1455 (m) cm$^{-1}$. $^1$H NMR (60 MHz, $CCl_4$): $\delta$ 7.18 (5 H, s), 4.2 – 3.7 (4 H, dq), 3.52 (2 H, s), 2.9 – 2.0 (7 H, m), 1.4 – 0.9 (9 H, dt + m).

*(RS)-Ethyl N-methoxycarbonyl-N-(2-ethoxycarbonylethyl)-2-methyl-3-aminopropionate* (3b). A solution of *2b* (79.95 g; 250 mmol) and aqueous hydrochloric acid (62.5 ml; 4 M) in ethanol (200 ml) was hydrogenated (*ca.* 250 kPa) in a PARR hydrogenation apparatus by using a 10 % Pd-C catalyst (5.6 g). The reaction mixture was filtered and evaporated *in vacuo*. To an ice-cooled solution of the residue in water (100 ml) was added with stirring an iced solution of potassium carbonate (86.94 g; 630 mmol) in water (100 ml) followed by addition of methyl chloroformate (28.20 g; 300 mmol). Stirring was continued at 0 °C for 30 min and at 25 °C for 1 h. The mixture was extracted with ether (3 × 200 ml). The combined and dried ($K_2CO_3$) ether phases were evaporated *in vacuo* and the residue distilled to give *3b* (46.4 g; 64 %), b.p. 143 – 145 °C/53 Pa. Anal. $C_{13}H_{23}NO_4$: C, H, N. IR (film): 2980 (m), 1730 (s), 1705 (s), 1485 (m), 1445 (m), 1410 (m) cm$^{-1}$. $^1$H NMR (60 MHz, $CCl_4$): $\delta$ 4.02 (4 H, q, *J* 7 Hz), 3.59 (3 H, s) 3.5 – 3.1 (4 H, m), 3.0 – 2.0 (3 H, m), 1.4 – 0.8 (9 H, m).

*(RS)-Ethyl 1-methoxycarbonyl-4-hydroxy-5-methyl-1,2,5,6-tetrahydropyridine-3-carboxylate* (4b). To a suspension of sodium (1.84 g; 80 mmol) in benzene-xylene (10:1) (80 ml) was added ethanol (9.2 g; 200 mmol). When the sodium was dissolved a solution of *3b* (23.2 g; 80 mmol) in benzene (40 ml) was added with stirring. The reaction mixture was left for 3 days at 25 °C. Upon addition of hydrochloric acid (25 ml; 4 M) the organic phase was dried ($Na_2SO_4$) and evaporated *in vacuo* to give crude *4b* (14.3 g). CC [silica gel: 400 g; eluents: benzene containing ethyl acetate (5 – 15 %)] followed by distillation gave *4b* (8.1 g; 42 %), b.p. 124 – 128 °C/40 Pa. Anal. $C_{11}H_{17}NO_5$: C, H, N. IR (film): 2980 (w), 2870 (w), 1710 (s), 1655 (m), 1620 (m), 1450 (m), 1410 (m) cm$^{-1}$. $^1$H NMR (60 MHz, $CCl_4$): $\delta$ 12.17 (1 H, s), 4.6 – 3.8 (4 H, m), 3.8 – 3.0 (5 H, m), 2.7 – 2.1 (1 H, m), 1.6 – 0.7 (6 H, m).

*(3RS,4SR)-Ethyl 1-methoxycarbonyl-4-hydroxypiperidine-3-carboxylate* (5a). A solution of *4a*[15] (55.0 g; 0.24 mol) in ethanol (500 ml) was hydrogenated (*ca.* 10 MPa) by using a Ra-Ni W-2 catalyst (9 g). The filtered and evaporated reaction product was distilled to give *5a* (50.0 g; 90 %), b.p. 145 – 149 °C/9 Pa, m.p. 51.5 – 53.5 °C. Anal. $C_{10}H_{17}NO_5$: C, H, N. IR (film): 3600 – 3200 (m), 2990 – 2850 (several bands, m), 1725 (s), 1705 (s) cm$^{-1}$.

*(3RS,4SR)-Dimethyl 4-hydroxypiperidine-1,3-dicarboxylate* (6a). A solution of *5a* (26 g; 0.11 mol) in a methanolic solution of hydrogen chloride (500 ml; 5 %) was refluxed for 18 h. The evaporated reaction mixture was distilled to give *6a* (21.0 g; 86 %), b.p. 143 – 146 °C/9 Pa, m.p. 68.5 – 70.5 °C. Anal. $C_9H_{15}NO_5$: C, H, N. IR (KBr): 3450 (s), 3000 – 2830 (several bands, m), 1720 (s), 1685 (s), 1670 (s) cm$^{-1}$.

*(3RS,4SR)-3-Carboxy-4-hydroxypiperidinium chloride* (7a). A solution of *6a* (4.0 g; 18.4 mmol) in hydrochloric acid (40 ml; 5 M) was refluxed for 150 min. The evaporated oily reaction product was crystallized from water-glacial acetic acid [35 ml; 2:5)] to give *7a* (1.6 g;

48 %), m.p. 170.0 – 172.0 °C. Anal. $C_5H_{12}ClNO_3$: C, H, Cl, N. IR (KBr): 3600 – 3350 (s), 3160 – 2740 (several bands, s), 2720 – 2400 (several bands, m), 1720 (s), 1600 (m) $cm^{-1}$. $^1H$ NMR (60 MHz, $D_2O$): $\delta$ 4.6 – 4.4 (1 H, m), 3.5 – 2.8 (5 H, m), 2.2 – 1.8 (2 H, m).

*(3RS,4SR)-4-Hydroxypiperidine-3-carboxylic acid zwitterion (8a)*. To a solution of *7a* (1.32 g; 10 mmol) in water (5 ml) was added a solution of triethylamine (1.06 g; 10.5 mmol) in ethanol (5 ml). To the filtered solution was added *N,N*-dimethylformamide (4 ml). Upon standing at 25 °C for 7 days *8a* (890 mg; 61 %) was isolated, m.p. 253 – 255 °C (decomp.). Anal. $C_6H_{11}NO_3$: C, H, N. IR (KBr): 3210 (s), 3100 – 2200 (several bands, s), 1615 (s), 1550 (s), 1540 (s) $cm^{-1}$. $pK_A$ values ($H_2O$, 22 °C): 3.42 ± 0.05; 10.02 ± 0.05.

*(3RS,4SR,5SR)-Ethyl 1-methoxycarbonyl-4-hydroxy-5-methylpiperidine-3-carboxylate (5c) and (3RS,4SR,5RS)-ethyl 1-methoxycarbonyl-4-hydroxy-5-methylpiperidine-3-carboxylate (5d)*. A solution of *4b* (4.0 g; 16 mmol) in ethanol (130 ml) was hydrogenated (*ca.* 3 MPa) by using an Ra-Ni W-2 catalyst (3 g) for 23 h. The filtered and evaporated reaction mixture was shown by TLC [eluent: benzene-ethyl acetate (4:1)] to consist of two compounds ($R_F$ = 0.24 and 0.17). CC [silica gel: 200 g; eluents: benzene containing ethyl acetate (15 – 25 %)] of the crude product and ball-tube distillation of the separated components at 133 Pa (oven temperature 180 °C) gave pure *5c* and *5d*. *5c* (1.45 g; 37 %) had m.p. 79.0 – 79.5 °C. Anal. $C_{11}H_{19}NO_5$: C, H, N. IR (KBr): 3470 (m), 2950 (m), 2900 (m), 1725 (s), 1685 (s), 1480 (s), 1455 (m), 1440 (m), 1415 (m) $cm^{-1}$. $^1H$ NMR (60 MHz, $CDCl_3$): $\delta$ 4.4 – 3.9 (m) and 3.67 (s) (a total of 7 H), 3.4 – 2.0 (5 H, m), 1.9 – 0.8 (7 H, m). *5d* (1.12 g; 29 %) had m.p. 45 – 46 °C. Anal $C_{11}H_{19}NO_5$: C, H, N. IR (film): 3470 (m), 2955 (m), 2925 (m), 1730 (s), 1700 (s), 1685 (s), 1480 (m), 1445 (m), 1415 (m) $cm^{-1}$. $^1H$ NMR (60 MHz, $CDCl_3$): $\delta$ 4.10 (q, *J* 7 Hz) and 3.9 – 2.2 (m) (a total of 12 H), 2.2 – 1.5 (1 H, m), 1.5 – 0.7 (6 H, m).

*(3RS,4SR,5SR)-Dimethyl 4-hydroxy-5-methylpiperidine-1,3-dicarboxylate (6c)*. A solution of *5c* (531 mg; 2.2 mmol) in methanolic hydrogen chloride (10 ml; 5 %) was refluxed for 17 h. Ball-tube distillation of the evaporated reaction product at 133 Pa (oven temperature 180 °C) gave *6c* (472 mg; 93 %), m.p. 30.0 – 31.0 °C. The IR spectrum was almost identical with that of *5c*.

*(3RS,4SR,5SR)-3-Carboxy-4-hydroxy-5-methylpiperidinium chloride (7c)*. A solution of *6c* (1.25 g; 5.4 mmol) in aqueous hydrochloric acid (50 ml; 5 M) was refluxed for 75 min. Evaporation of the reaction mixture *in vacuo* and recrystallization (water – acetic acid) of the residue gave *7c* (486 mg; 46 %), m.p. 232.5 – 233.5 °C. Anal. $C_7H_{14}ClNO_3$: C, H, Cl, N. IR (KBr): 3400 (m), 3145 (m), 2940 (m), 2800 (m), 1720 (s), 1605 (m), 1465 (m), 1450 (m), 1420 (m) $cm^{-1}$. $^1H$ NMR (60 MHz, $D_2O$): $\delta$ 4.23 (1 H, slightly broadened s), 3.6 – 2.5 (5 H, m), 2.3 – 1.6 (1 H, m), 1.00 (3 H, d, *J* 7 Hz).

*(3RS,4SR,5SR)-4-Hydroxy-5-methylpiperidine-3-carboxylic acid zwitterion (8c)*. To a solution of *7c* (100 mg; 0.51 mmol) in water (1 ml) was added a solution of triethylamine (57 mg; 0.56 mmol) in ethanol (1 ml). The mixture was left at 4 °C for 17 h. Recrystallization (water – ethanol) of crude *8c* gave pure *8c* (46 mg; 51 %), m.p. 116.0 – 117.0 °C. Anal. $C_7H_{13}NO_3,H_2O$: C, H, N. IR (KBr): 3700 – 3100 (s), 3100 – 2400 (several bands, m), 1590 (s), 1470 (m), 1395 (s) $cm^{-1}$. $pK_A$ values ($H_2O$, 23 °C): 3.39 ± 0.02; 10.13 ± 0.04.

*(3RS,4SR,5RS)-Dimethyl 4-hydroxy-5-methylpiperidine-1,3-dicarboxylate (6d)*. *6d* was synthesized as described above for *6c* by using *5d* (471 mg; 1.9 mmol) as a starting material. Purification of the crude product by ball-tube distillation at 133 Pa (oven temperature 180 °C) gave *6d* (404 mg; 92 %). The IR spectrum was almost identical with that of *5d*.

*(3RS,4SR,5RS)-3-Carboxy-4-hydroxy-5-methylpiperidinium chloride (7d)*. *7d* was synthesized as described above for *7c* by using *6d* (1.25 g; 5.4 mmol) as a starting material. Recrystallization (water – acetic acid) of the crude product gave *7d* (297 mg; 28 %), m.p. 211.5 – 212.0 °C. Anal. $C_7H_{14}ClNO_3$: C, H, Cl, N. IR (KBr): 3445 (m), 3110 (m), 3000 (m), 2845 (m), 1720 (s), 1585 (m), 1470 (m), 1435 (m) $cm^{-1}$. $^1H$ NMR (60 MHz, $D_2O$): $\delta$ 4.0 – 3.7 (1 H, m), 3.7 – 2.6 (5 H, m), 2.4 – 1.8 (1 H, m), 1.07 (3 H, d, *J* 7 Hz).

*(3RS,4SR,5RS)-4-Hydroxy-5-methylpiperidine-3-carboxylic acid zwitterion (8d)*. *8d* was synthesized as described above for *8c* by using *7d* (100 mg; 0.51 mmol) as a starting material. Recrystallization (water-ethanol) of the crude product gave *8d* (28 mg; 31 %), m.p. 234.0 – 235.0 °C. Anal. $C_7H_{13}NO_3,H_2O$: C, H, N. IR (KBr): 3600 – 3350 (m), 3350 – 2800 (several bands, s – m), 1730 (m), 1600 (s), 1470 (m), 1410 (s) $cm^{-1}$. $pK_A$ values ($H_2O$, 23 °C): 3.28 ± 0.03; 9.99 ± 0.06.

*Guvacine hydrobromide (3-carboxy-1,2,5,6-tetrahydropyridinium bromide) (9a)*. A solution of *6a* (13.5 g; 62 mmol) in aqueous hydrobromic acid (60 ml; 48 %) was refluxed for 24 h. Upon cooling of the reaction mixture to 5 °C pure *9a* (10.4 g; 30 %) crystallized, m.p. 230 °C (decomp.). Anal. $C_6H_{10}BrNO_2$: C, H, Br, N. IR (KBr): 3175 (m), 2950 (s), 2820 (m), 2620 – 2400 (several bands, w), 1720 (s), 1660 (m), 1580 (m) $cm^{-1}$. UV [methanol (log $\varepsilon$)]: 212 (4.00) nm. $^1H$ NMR (60 MHz, $D_2O$): $\delta$ 7.3 – 7.0 (1 H, m), 3.9 – 3.7 (2 H, q), 3.5 – 3.1 (2 H, t), 2.7 – 2.3 (2 H, m). $pK_A$ values ($H_2O$, 22 °C): 3.50 ± 0.06; 9.85 ± 0.06.

*(RS)-3-Carboxy-5-methyl-1,2,5,6-tetrahydropyridinium bromide (9b)*. A solution of *6c* (517 mg; 1.99 mmol) in aqueous hydrobromic acid (1.5 ml; 48 %) was refluxed for 24 h. Upon cooling of the reaction mixture to 24 °C TLC-pure *9b* crystallized (162 mg; 37 %) [$R_F$:

0.22; eluent: 1-butanol – acetic acid – water (4:1:1)]. An analytical sample was recrystallized (water – acetic acid) to give *9b*, m.p. 253.5 – 254.5 °C. Anal. $C_7H_{12}BrNO_2$: C, H, Br, N. IR (KBr): 3550 – 3300 (m), 3250 – 2500 (several bands, s – m), 1710 (s), 1660 (m), 1605 (m), 1400 (m) $cm^{-1}$. UV [methanol (log $\varepsilon$)]: 214 (4.00) nm. $^1H$ NMR (60 MHz, $D_2O$): $\delta$ 7.2 – 6.9 (1 H, m), 3.9 – 3.7 (2 H, broadened s), 3.7 – 3.2 (1 H, m), 3.1 – 2.5 (2 H, m), 1.17 (3 H, d, $J$ 7 Hz).

*(RS)-5-Methyl-1,2,5,6-tetrahydropyridine-3-carboxylic acid zwitterion (10)*. *10* was synthesized as described above for *3c* by using *9b* (100 mg; 0.56 mmol) and a solution of triethylamine (63 mg; 0.62 mmol) in ethanol (2 ml). Recrystallization (water – ethanol) of the crude product gave *10* (37 mg; 47 %), m.p. 249.0 – 249.5 °C. Anal. $C_7H_{11}NO_2$: C, H, N. IR (KBr): 3600 – 3250 (m), 3200 – 2000 (several bands, m), 1660 (s), 1630 (s), 1550 (s), 1470 (m) $cm^{-1}$. UV [methanol (log $\varepsilon$)]: 210 (3.38) nm. $pK_A$ values ($H_2O$, 23 °C): 3.29 ± 0.03; 9.35 ± 0.03.

*(3RS,4SR)-Dimethyl 4-hydroxyperhydroazepine-1,3-dicarboxylate (12) and (3RS,4RS)-dimethyl 4-hydroxyperhydroazepine-1,3-dicarboxylate (13)*. A mixture of *12* and *13* was prepared from *11* [16] (2.56 g; 10.5 mmol) in ethanol (15 ml) by using 1.5 g of catalyst as described above for *3c,d*, followed by reflux of a solution of the crude reduction product in methanolic hydrogen chloride (150 ml; 15 %) for 24 h. CC [silica gel: 180 g; eluents: benzene containing ethyl acetate (15 – 25 %)] of the evaporated reaction product followed by ball-tube distillation at 60 Pa (oven temperature 180 °C) of the isolated components gave *12* (1.68 g; 69 %), m.p. 55.5 – 57.5 °C. Anal. $C_{10}H_{17}NO_4$: C, H, N. IR (KBr): 3450 (m), 2950 (m), 2930 (m), 1735 (s), 1705 – 1675 (s), 1485 – 1440 (m), 1410 (m) $cm^{-1}$. 349 mg (14 %) of *13* was obtained. Anal. $C_{10}H_{17}NO_4$: C, H, N. IR (film): 3450 (m), 2950 (m), 2930 (m), 1735 (s), 1705 – 1680 (s), 1485 – 1440 (m), 1410 (m) $cm^{-1}$.

*3-Carboxy-2,5,6,7-tetrahydro-1H-azepinium bromide (14)*. A solution of *12* (370 mg; 1.6 mmol) in hydrobromic acid (1 ml; 48 %) was refluxed for 24 h. Evaporation *in vacuo* and recrystallization (water – isopropanol) of the residue gave *14* (225 mg; 63 %), m.p. 224.5 – 225.5 °C. Anal. $C_7H_{12}BrNO_2$: C, H, Br, N. IR (KBr): 3430 (m), 3150 – 2700 (several bands, s – m), 1715 (s), 1650 (m), 1575 (m), 1460 (m), 1420 (m) $cm^{-1}$. UV [methanol (log $\varepsilon$)]: 210 (4.00) nm. $^1H$ NMR (60 MHz, $D_2O$): $\delta$ 7.55 (1 H, t, $J$ 7 Hz), 4.12 (2 H, s), 3.6 – 3.3 (2 H, m), 2.8 – 2.3 (2 H, m), 2.2 – 1.6 (2 H, m). $pK_A$ values ($H_2O$, 23 °C): 3.71 ± 0.05; 10.20 ± 0.03.

*(RS)-3-Carboxyperhydroazepinium bromide (15)*. A solution of *14* (490 mg; 2.2 mmol) in aqueous ethanol (150 ml; 35 %) was hydrogenated (*ca.* 300 kPa) in a PARR hydrogenation apparatus by using a 10 % Pd – C catalyst (100 mg). Evaporation *in vacuo* and recrystallization of the residue (water – acetic acid) gave *15* (368 mg; 74 %), m.p. 145.0 – 146.5 °C. Anal. $C_7H_{14}BrNO_2$: C, H, Br, N. IR (KBr): 3700 – 3300 (m), 3250 – 2900 (s), 2860 (m), 2750 – 2400 (several bands, m – w), 1730 (s), 1580 (m) $cm^{-1}$. $^1H$ NMR (60 MHz, $D_2O$): $\delta$ 3.7 – 2.9 (5 H, m), 2.4 – 1.6 (6 H, m). $pK_A$ values ($H_2O$, 23 °C): 3.33 ± 0.04; 10.58 ± 0.04.

*(1R,2R,3S,5S)-(–)-Methyl 3-ethoxycarbonyloxy-8-ethoxycarbonylnortropane-2-carboxylate (17)*. A solution of ecgonine hydrate (*16*) (3.0 g; 14.8 mmol) in methanolic hydrogen chloride (200 ml; 5 %) was refluxed for 4 h. Upon evaporation *in vacuo* an aqueous solution (7 ml) of the residue, adjusted to pH 10 by sodium hydroxide, was extracted with chloroform (3 × 30 ml). The combined, dried ($Na_2CO_3$), and evaporated organic phases were submitted to ball-tube distillation at 130 Pa (oven temperature 150 °C) to give ecgonine methyl ester (2.5 g; 85 %) as a TLC-pure oil [$R_F$: 0.11; eluent: 1-butanol – acetic acid – water (4:1:1)]. A solution of ecgonine methyl ester (2.5 g; 12.6 mmol) and ethyl chloroformate (14.0 g; 130 mmol) in 1,2-dichloroethane (70 ml) was refluxed for 3 days. Evaporation *in vacuo* and CC [silica gel: 180 g; eluents: dichloromethane containing ethyl acetate (20 – 50 %) and methanol (3 %)] of the oily residue followed by ball-tube distillation at 100 Pa (oven temperature 170 °C) gave *17* (1.63 g; 39 %), m.p. 92.0 – 93.5 °C. Anal. $C_{13}H_{23}NO_7$: C, H, N. $[\alpha]_D^{25}$ – 48° (*c* 0.91, ethanol). IR (KBr): 3600 – 3100 (m), 2980 (m), 2890 (w), 1735 (s), 1710 (s), 1480 (m), 1435 (s) $cm^{-1}$. $^1H$ NMR (60 MHz, $CCl_4$): $\delta$ 5.2 – 4.7 (1 H, m), 4.7 – 4.3 (2 H, m), 4.3 – 3.8 (4 H, dq, each $J$ 7 Hz), 3.66 (3 H, s), 3.1 – 2.3 (2 H, q), 2.7 – 2.2 (1 H, m), 2.0 – 1.6 (4 H, m), 1.5 – 1.2 (6 H, dt, each $J$ 7 Hz).

*(1R,5S)-(–)-2-Nortropene-2-carboxylic acid hydrobromide (18)*. A solution of *17* (825 mg; 2.5 mmol) in aqueous hydrobromic acid (6 ml; 48 %) was refluxed for 5 h. Evaporation *in vacuo* and recrystallization (2-propanol – ether) of the residue gave *18* (389 mg; 66 %), m.p. 278.5 – 280.5 °C. Anal. $C_8H_{12}BrNO_2$: C, H, Br, N. $[\alpha]_D^{25}$ – 61° (*c* 0.98, water). IR (KBr): 3080 (s), 2890 (s), 2730 – 2440 (several bands, m – w), 1690 (s), 1640 (m), 1600 (m) $cm^{-1}$. UV [methanol (log $\varepsilon$)]: 212 (3.95) nm. $^1H$ NMR (60 MHz, $D_2O$): $\delta$ 7.2 – 7.0 (1 H, t, $J$ 4 Hz), 4.8 – 4.6 (1 H, m), 4.5 – 4.2 (1 H, m), 3.4 – 2.4 (2 H, m), 2.4 – 1.9 (4 H, m). $pK_A$ values ($H_2O$, 23 °C): 3.33 ± 0.03; 10.23 ± 0.05.

*(1R,2R,5R)-(+)-Nortropane-2-carboxylic acid hydrobromide (19)*. *19* was prepared as described above for *15* from *18* (250 mg; 1.1 mmol) by using 50 mg of the catalyst. 203 mg (81 %) of *19* was obtained, m.p. 237.5 – 238.5 °C. Anal. $C_8H_{14}BrNO_2$: C, H, Br, N. $[\alpha]_D^{25}$ + 12 ° (*c* 0.98, water). IR (KBr): 3600 – 3300 (m), 3120 (m), 3000 – 2930 (s), 2800 – 2400 (several bands, m – w), 1730 (s), 1610 (m) $cm^{-1}$.

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# Total synthesis of balanol: a potent protein kinase C inhibitor of fungal origin

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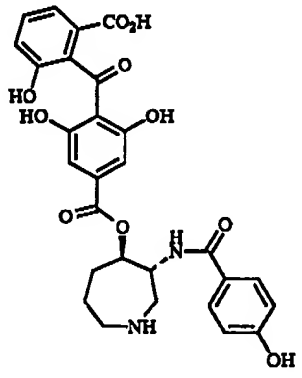
The total synthesis of the fungal metabolite balanol, a potent inhibitor of protein kinase C, is described. The synthesis includes a novel synthesis of 3-amino-4-hydroxyazepanes *via* a directed ring expansion of 3-bromopiperidin-4-ones.

Balanol **1** is a structurally novel inhibitor of protein kinase C, a family of phospholipid dependent serine/threonine protein kinases which play an important role in cell growth, signal transduction and differentiation.[1] The activated enzyme[2] has been implicated in many diseases, such as cancer, inflammation and HIV infection; therefore inhibitors of protein kinase C may be therapeutic.[3] Balanol **1** was initially isolated by workers at Sphinx Pharmaceuticals from *Verticillium balanoides*[4,5] and more recently from species of *Fusarium*[6] by a team at Nippon Roche. Synthetic interest in balanol is intense, owing to its chemical structure, biological activity and its low availability from natural sources. As our synthetic route was nearing completion, the total synthesis of balanol was recently reported by workers at Sphinx,[7] and by the Nicolaou group.[8] Here we describe a new synthesis of balanol with novel routes to the hexahydroazepine (azepane) and benzophenone portions.



**1**

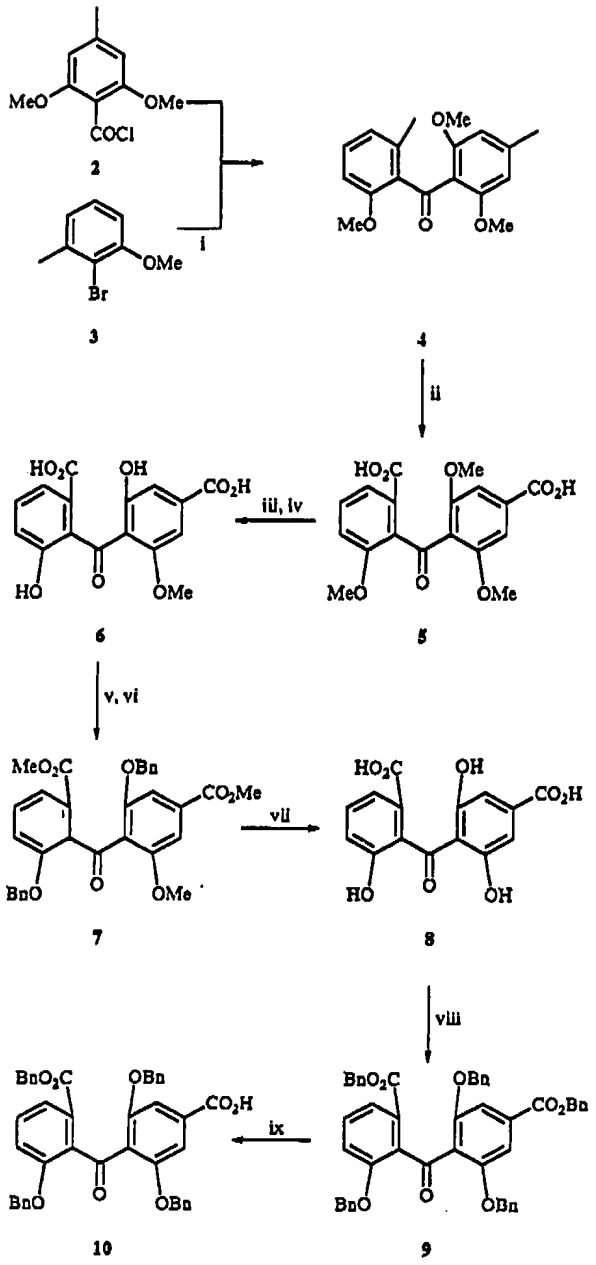
## Results and discussion

The key disconnection for the synthesis of balanol is the ester bond joining the azepane and the benzoic acid. This implies that preparation of suitably protected benzophenone and azepane portions, which would be coupled together to form the ester bond, could then be deprotected to give balanol **1**.

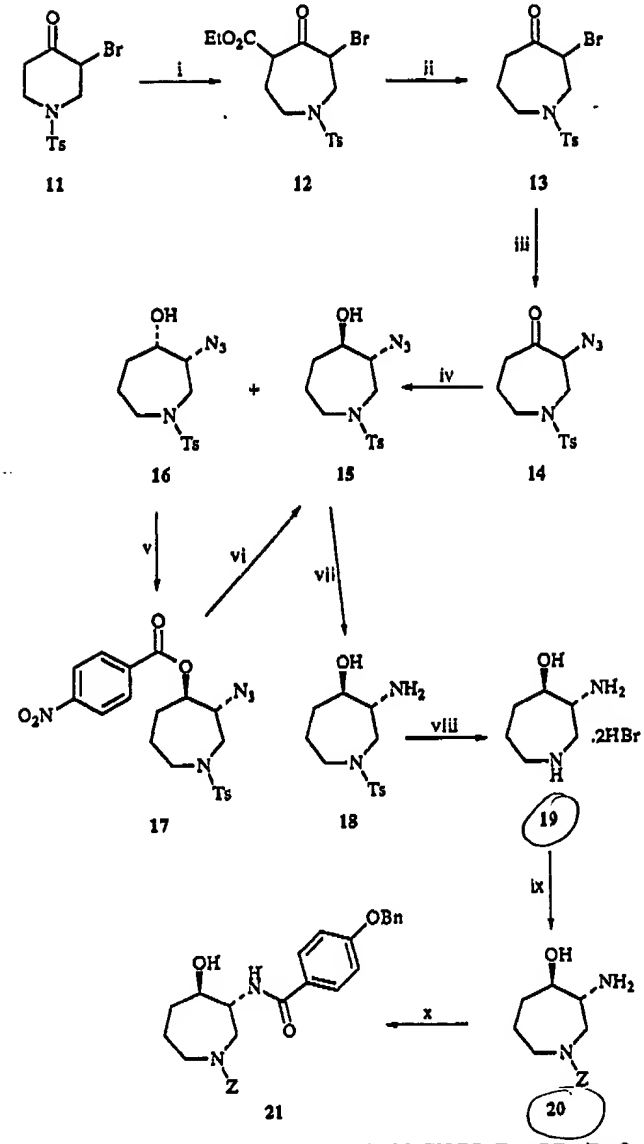
The synthesis of the benzophenone portion started from 2,6-dimethoxy-4-methylbenzoyl chloride[9] **2** and 2-bromo-3-methoxytoluene[10] **3** which were readily prepared from commercially available 3,5-dimethoxytoluene and 2-amino-3-methoxytoluene respectively, in 86 and 85% yield. Formation of the Grignard reagent of **3** and reaction of this with **2** gave the hindered benzophenone **4** in 80% yield. Oxidation of the methyl groups of **4** using potassium permanganate gave the diacid **5** in 38% yield. The diacid **5** had limited solubility and was quantitatively converted into the dimethyl ester. Treatment of this dimethyl ester with boron tribromide gave **6** in 95% yield with only small amounts of **8** being detected. Further demethylation of **6** to give the triphenolic diacid **8** directly was problematic and treatment of **6** with boron tribromide and a host of other demethylating agents yielded only traces of **8**. Possibly once **6** has been formed, its insolubility and ability to complex with reagents hinders the final demethylation. This problem was overcome by re-esterification of **6** to give the dimethyl ester followed by benzylation of the phenolic groups to give **7** in 74% overall yield. Treatment of **7** with boron tribromide in dichloromethane gave the desired triphenolic diacid **8** in 52% yield and **6** in 41% yield which could be recycled. In this case, the demethylation occurred competitively with the more hindered benzyl groups, which, since they are more labile than the methoxy group, are then subsequently removed. Complete demethylation of the dimethyl ester of **6** under the above conditions was unsuccessful, only ester hydrolysis being observed. The triphenolic diacid **8** was converted into the pentabenzyl compound **9** in 42% yield selective hydrolysis of which gave **10** in 91% yield. This compound was identical spectroscopically with an authentic sample prepared by a different route.[7d,8] The tetrabenzyl compound **10** is suitably protected for activation and coupling to a protected portion of the azepane **21** to give balanol.

The synthesis of the azepane portion of balanol started from commercially available piperidin-4-one. *N*-Tosylation under standard conditions followed by bromination gave **11** in 80% overall yield. The tosyl group was chosen to protect the nitrogen as this group was more stable to the bromination conditions and subsequent stages than carbamates and all compounds containing the tosyl group were crystalline. It was expected that the tosyl group would have to be removed and replaced by a more labile group after the requisite functional group manipulations had been completed so that deprotection at the final stage of the balanol synthesis would not be problematic.

The regiospecific homologation of unhindered α-bromo ketones using ethyl diazoacetate and boron trifluoride–diethyl ether has been reported.[11] The observed regioselectivity of homologation has been demonstrated to be due to a combination of steric and electronic factors.[11] The electron-withdrawing effect of the α-bromo substituent suppresses the migration of the carbon atom bearing it and the steric effect of the bromine atom enhances this selectivity of migration. This



Scheme 1 *Reagents and conditions:* i, Mg, THF, 2 (80%); ii, $KMnO_4$, pyridine (aq.) (38%); iii, $SOCl_2$, MeOH, iv, $BBr_3$, $CH_2Cl_2$ (95% from 5); v, $SOCl_2$, MeOH; vi, NaH, BnBr, DMF (74% from 6); vii, $BBr_3$, $CH_2Cl_2$ (52%); viii, NaH, BnBr, DMF (42%); ix, $Na_2CO_3$ (aq.), EtOH (91%)



Scheme 2 *Reagents and conditions:* i, $N_2CHCO_2Et$, $BF_3$–$Et_2O$, $CH_2Cl_2$ (71%); ii, HCl (aq), dioxane (90%); iii, $NaN_3$, AcOH, DMF (73%); iv, $NaBH_4$, EtOH (88%); v, $PPh_3$, DIAD, THF, *p*-nitrobenzoic acid (84%); vi, NaOH (aq.), MeOH, dioxane (99%); vii, $LiAlH_4$, THF (85%); viii, HBr (aq.) (68%); ix, $Et_3N$, $CH_2Cl_2$, 18-crown-6, benzyl chloroformate (88%); x, 4-(benzyloxy)benzoyl chloride, $Et_3N$, $CH_2Cl_2$ (65%)

sort of regiospecific homologation has not been applied previously to unsymmetrical ketones present in heterocyclic systems. A novel use of this type of ring expansion was demonstrated in the conversion of **11** into **12** using ethyl diazoacetate under Lewis acid conditions, which proceeded in 71% yield. As predicted, insertion of the methylene was selective for the unhindered side of the ketone, with none of the other regioisomer being observed. Hydrolysis and decarboxylation of **12** gave **13** in 90% yield. Reaction of **13** with sodium azide resulted in nucleophilic displacement of bromide by azide to give **14** in 73% yield. Reduction of **14** with sodium boranuide ($NaBH_4$) gave a *cis*:*trans* (2.4:1) mixture of azido alcohols **16** and **15** which were easily separable by chromatography giving **15** in 26% and **16** in 62% yields, respectively. Conversion of the major unwanted *cis* isomer **16** into the *trans* isomer **15** proceeded in 84% yield using a Mitsunobu[12] inversion *via* the *p*-nitrobenzoate **17** followed by hydrolysis. The *trans* relationship of the hydroxy and azido groups in **15** was unambiguously established by X-ray crystallography at this stage as shown in Fig. 1. Treatment of **15** with lithium aluminium hydride gave the 3-amino-4-hydroxyazepane **18** in 85% yield. At this stage, the *N*-tosyl group had to be replaced by a group that would be more easily removed in the final stage of the synthesis. Removal of the *N*-tosyl group was effected in 68% yield using aqueous hydrobromic acid to give **19**. Selective protection of the secondary amino group in **19** proceeded in 88% yield using benzyl chloroformate in the presence of 18-crown-6 to give **20**. Reaction of **20** under standard conditions with 4-(benzyloxy)benzoyl chloride gave **21** in 65% yield, which is a suitably protected azepane portion of balanol to be coupled to **10** following activation. The enantiomers of **21** were resolved by forming their Mosher's esters[13] **22** followed by chromatography and hydrolysis to give both enantiomers of **21** in

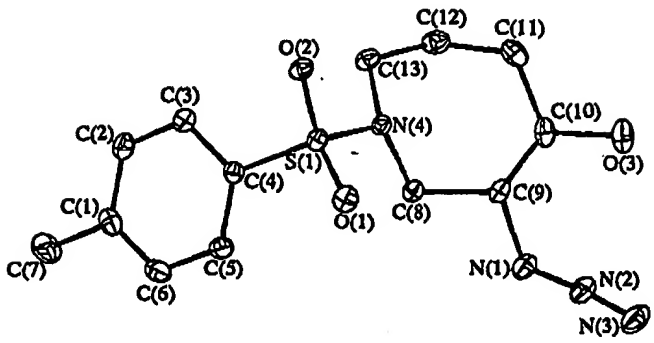
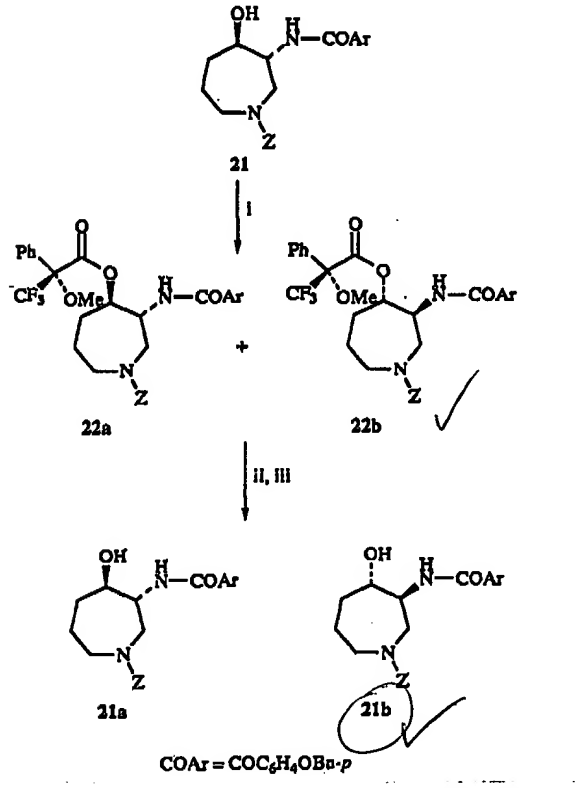


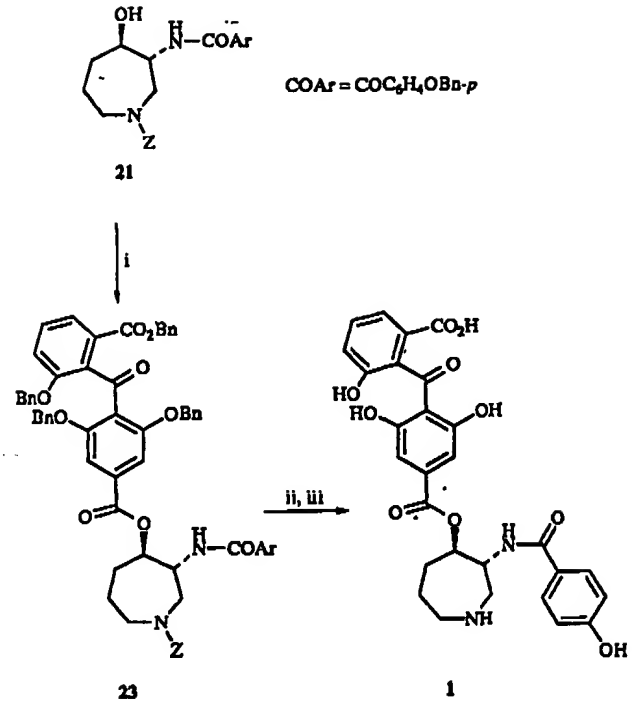

Fig. 1 X-Ray structure of compound 15




Scheme 3 *Reagents and conditions:* i, acid chloride of (*S*)-(-)-MTPA; $CH_2Cl_2$, $Et_3N$, DMAP; ii, chromatography (96% from **21**); iii, KOH, MeOH (100%)

96% overall yield and in >99% ee. The enantiomeric purity was checked relative to the racemate using chiral chromatography. This separation allowed access to both enantiomerically pure forms of balanol in a similar manner to that previously described.[7a] Compound **21** was identical with an authentic sample prepared by a different route.[8]

Activation of **10** by the method of Mukaiyama,[14] as employed in the Nicolaou synthesis[8] of balanol followed by coupling to **21** gave **23** which was identical spectroscopically with an authentic sample.[8] Hydrogenolysis of **23** with palladium black in aqueous acetic acid–ethyl acetate gave balanol **1** as a major product. In our hands the use of THF as a co-solvent under similar conditions to Nicolaou during the deprotection step gave rise to quantities of *N*-hydroxybutylbalanol. This side reaction was avoided by replacing the THF with ethyl acetate. Purification of **1** using reverse phase HPLC gave pure balanol **1** identical by HPLC, MS and NMR with an authentic sample of balanol.[8]




Scheme 4 *Reagents and conditions:* i, **10**, 2-chloro-1-methylpyridinium iodide, DMAP, $Et_3N$, $CH_2Cl_2$ (37%); ii, $H_2$, Pd black, HOAc, EtOAc, $H_2O$; iii, HPLC (53% from **23**)

## Experimental

Mps were determined using an Electrothermal apparatus and are uncorrected. IR spectra were recorded on a Nicolet 20SXB spectrophotometer. $^1H$ NMR spectra were obtained using a Varian VXR400 instrument (400 MHz), $\delta$ values quoted are relative to internal TMS and $J$ values are given in Hz. Mass spectra were measured with either a Varian VG 7070E or Finnegan TSQ 700 spectrometer. Flash chromatography was performed using Sorbsil C 60 (40–60 μm mesh) silica gel. Analytical thin layer chromatography was carried out on 0.25 mm precoated silica gel plates (E. Merck Kieselgel 60 $F_{254}$) and compounds were visualised using UV fluorescence, ethanolic phosphomolybdic acid or aqueous potassium permanganate.

### 2,6-Dimethoxy-4-methylphenyl 2-methoxy-6-methylphenyl ketone 4

A suspension of magnesium turnings (0.6 g, 25 mmol) in THF (2 $cm^3$) under an atmosphere of nitrogen was treated with 1,2-dibromoethane (0.14 $cm^3$). The mixture was slowly stirred and heated to reflux whilst a solution of 2-bromo-3-methoxytoluene **3** (5.03 g, 25 mmol) in THF (20 $cm^3$) was added dropwise. The mixture was heated at reflux for 1 h, allowed to cool to room temperature and then filtered to remove any traces of magnesium. To this Grignard reagent a solution of 2,6-dimethoxy-4-methylbenzoyl chloride **3** (5.25 g, 25 mmol) in THF (20 $cm^3$) was added dropwise, the temperature of the mixture being kept at *ca.* 25 °C. The mixture was stirred at room temperature for 30 min after which the solvent was removed under reduced pressure to give a pale red syrup which was treated with saturated aq. $NH_4Cl$ (200 $cm^3$) and ethyl acetate (150 $cm^3$). The layers were separated and the aqueous layer was extracted with ethyl acetate (50 $cm^3$). The combined organic layer and extracts were washed with 5% aq. $NaHCO_3$ (3 × 100 $cm^3$) and brine (100 $cm^3$) dried ($MgSO_4$), filtered and evaporated under reduced pressure to yield a yellow solid (7.2

g). This was recrystallised from ethanol to yield **4** (6.0 g, 80%) as a white solid, mp 132–133 °C (Found: C, 71.8; H, 6.6. $C_{18}H_{20}O_4$ requires C, 72.0; H, 6.7%); $\nu_{max}$(KBr)/cm$^{-1}$ 1670s (CO); $\delta_H$($CDCl_3$) 2.31 (3 H, s, Me), 2.34 (3 H, s, Me), 3.58 (3 H, s, 6-OMe), 3.66 (6 H, s, 2'- and 6'-OMe), 6.34 (2 H, s, 3'- and 5'-H), 6.67 (1 H, d, *J* 8), 6.78 (1 H, d, *J* 8) and 7.16 (1 H, t, *J* 8, 4-H); *m/z* 301 ($MH^+$).

**4-Carboxy-2,6-dimethoxyphenyl 2-carboxy-6-methoxyphenyl ketone 5**

To a stirred solution of potassium permanganate (28 g, 3 equiv.) in water (160 cm$^3$) and pyridine (160 cm$^3$) at *ca.* 100 °C, aq. NaOH (20%; 4 cm$^3$) was added. To this stirred mixture a solution of **4** (17.67 g, 16.98 mmol) in pyridine (90 cm$^3$) was added dropwise followed by water (90 cm$^3$). The mixture was heated at reflux for 1 h after which further quantities of potassium permanganate (28 g, 3 equiv.) were added hourly to it, stirring and heating being continued, until a total of 208 g, 24 equiv. had been added. The hot reaction mixture was filtered through Celite and the filter cake was washed with water (4 × 150 cm$^3$) and pyridine (50 cm$^3$). The filtrate was cooled on ice and acidified to pH 1 by the addition of concentrated aq. HCl; any precipitated solid was filtered off. The acidic aqueous filtrate was treated with NaCl (200 g) and extracted with ethyl acetate (6 × 400 cm$^3$). The combine/extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure and the residue treated with diethyl ether to give **5** (8.1 g, 38%) as a white solid, mp 253–256 °C (Found: C, 59.1; H, 4.5. $C_{18}H_{16}O_8$·0.25$H_2O$ requires C, 59.25; H, 4.4%); $\nu_{max}$(KBr)/cm$^{-1}$ 3400br and 2900br (OH), 1690s (CO); $\delta_H$($CD_3SOCD_3$) 3.59 (3 H, s, 6-OMe), 3.64 (6 H, s, 2'- and 6'-OMe), 7.17 (2 H, s, 3'- and 5'-H), 7.22 (1 H, d, *J* 8), 7.29 (1 H, d, *J* 8) and 7.46 (1 H, t, *J* 8, 4-H); *m/z* 361 ($MH^+$).

**4-Carboxy-2-hydroxy-6-methoxyphenyl 2-carboxy-6-hydroxyphenyl ketone 6**

To a stirred solution of **5** (1.01 g, 2.8 mmol) in methanol (25 cm$^3$), thionyl chloride (1.17 cm$^3$, 16 mmol) was added dropwise and the mixture heated at reflux for 2 h. The mixture was allowed to cool to room temperature and then evaporated to dryness. Treatment of the residue with toluene (2 × 20 cm$^3$) and removal of the solvent gave a white solid (1.09 g) which was dissolved in dichloromethane (37 cm$^3$) and the resulting solution was cooled to −60 °C. To the solution at −60 °C boron tribromide in dichloromethane (1 mol dm$^{-3}$; 31 cm$^3$) was added dropwise and the mixture was allowed to warm to room temperature with stirring for 18 h. The mixture was cooled to 0 °C and water (50 cm$^3$) was added dropwise to it. The mixture was allowed to warm to room temperature and any precipitated solid was removed by filtration. The layers were separated and the aqueous layer was adjusted to pH 4 by the addition of aq. $NaHCO_3$ (5%) and the aqueous layer was re-extracted with ethyl acetate (2 × 50 cm$^3$). The solid removed by the previous filtration was dissolved in the combined organic extracts and the solution dried ($MgSO_4$), filtered and evaporated under reduced pressure to yield **6** (0.9 g, 95%) as a pale yellow solid, mp 262–265 °C (Found C, 57.8; H, 3.7. $C_{16}H_{12}O_8$ requires C, 57.8; H, 3.6%); $\nu_{max}$(KBr)/cm$^{-1}$ 3490br, 3415br and 2900br (OH), 1680s and 1635s (CO); $\delta_H$($CD_3SOCD_3$) 3.49 (3 H, s, 6'-OMe), 6.90 (1 H, s), 7.05 (1 H, s), 7.08 (1 H, d, *J* 8), 7.32 (1 H, t, *J* 8, 4-H), 7.39 (1 H, d, *J* 8), 9.90 (1 H, br s, OH) and 12.75 (1 H, br s; OH); *m/z* 333 ($MH^+$).

**2-Hydroxy-6-methoxycarbonylphenyl 2-hydroxy-6-methoxy-4-methoxycarbonylphenyl ketone**

To a stirred solution of **6** (5.64 g, 17 mmol) in methanol (200 cm$^3$) thionyl chloride (12 cm$^3$, 165 mmol) was added dropwise. The mixture was heated at reflux for 3 h, after which it was allowed to cool to room temperature and then evaporated to dryness to give a light brown crystalline solid. This was then treated first with toluene (2 × 20 cm$^3$) which was evaporated under reduced pressure and then with diethyl ether to give a cream crystalline solid (6.13 g, 100%), mp 154–156 °C (Found C, 59.8; H, 4.5. $C_{16}H_{16}O_8$ requires C, 60.0; H, 4.5%); $\nu_{max}$(KBr)/cm$^{-1}$ 3450br (OH), 1725s and 1710s (CO); $\delta_H$($CDCl_3$) 3.46 (3 H, s, 6'-OMe), 3.52 (3 H, s, $CO_2Me$), 3.83 (3 H, s, $CO_2Me$), 6.94 (1 H, s), 7.12 (1 H, d, *J* 8), 7.30 (1 H, s), 7.38 (1 H, t, *J* 8, 4-H), 7.44 (1 H, d, *J* 8); *m/z* 361 ($MH^+$).

**2-Benzyloxy-6-methoxycarbonylphenyl 2-benzyloxy-6-methoxy-4-methoxycarbonylphenyl ketone 7**

To a stirred solution of 2-hydroxy-6-methoxycarbonylphenyl 2-hydroxy-6-methoxy-4-methoxycarbonylphenyl ketone (6.13 g, 17 mmol) in dry DMF (120 cm$^3$) at 0 °C NaH (60% in oil; 2.04 g, 51 mmol) was added during 3 min. After the mixture had been allowed to warm to room temperature with stirring over 1 h benzyl bromide (6.5 cm$^3$, 51 mmol) was added to it and the reaction mixture was heated at 65 °C for 2 h. After the mixture had been cooled to 0 °C it was treated with methanol (10 cm$^3$) and then evaporated under reduced pressure; the residue was then treated with ice water (400 cm$^3$) and extracted with diethyl ether (2 × 150 cm$^3$). The combined extracts were dried ($MgSO_4$) filtered and evaporated under reduced pressure to yield a yellow solid. Treatment of this with diethyl ether gave **7** (7 g, 74%) as a cream solid, mp 155–158 °C (Found C, 71.1; H, 5.1. $C_{32}H_{28}O_8$ requires C, 71.1; H, 5.2%); $\nu_{max}$(KBr)/cm$^{-1}$ 1730s and 1670s (CO); $\delta_H$($CDCl_3$) 3.64 (3 H, s, 6'-OMe), 3.70 (3 H, s, $CO_2Me$), 3.95 (3 H, s, $CO_2Me$), 4.75 (2 H, s, $OCH_2Ph$), 4.86 (2 H, s, $OCH_2Ph$), 6.94 (3 H, m), 7.05 (2 H, m), 7.10 (1 H, s) and 7.15–7.35 (9 H, m); *m/z* 541 ($MH^+$).

**4-Carboxy-2,6-dihydroxyphenyl 2-carboxy-6-hydroxyphenyl ketone 8**

To a stirred solution of **7** (6 g, 11.1 mmol) in dichloromethane (150 cm$^3$) at −60 °C boron tribromide in dichloromethane (1 mol dm$^{-3}$; 122 cm$^3$) was added dropwise during 45 min. The reaction mixture was allowed to warm to room temperature after which it was kept at ambient temperature for 2 days. It was then cooled to 10 °C, treated dropwise with water (150 cm$^3$) and stirred at room temperature for 1 h. The layers were separated and the aqueous layer adjusted to pH 4 by the addition of solid $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (2 × 100 cm$^3$) and the combined extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure to yield a yellow solid. The residue was purified by column chromatography on silica, eluting with methanol–dichloromethane (5:95, v/v), to give **8** (1.85 g, 52% uncorrected) as a light yellow solid, mp 222–225 °C (Found C, 56.3; H, 3.2. $C_{15}H_{10}O_8$ requires C, 56.6; H, 3.2%); $\nu_{max}$(KBr)/cm$^{-1}$ 3500br, 3100br, 2900br and 2600br (OH), 1700s and 1640s (CO); $\delta_H$($CD_3SOCD_3$) 6.69 (2 H, s, 2'- and 6'-H), 7.06 (1 H, d, *J* 8), 7.27 (1 H, t, *J* 8, 4-H) and 7.48 (1 H, d, *J* 8; *m/z* 318 ($M^+$). A quantity of **6** was also recovered (1.5 g, 41%) which could be recycled.

**2-Benzyloxy-6-benzyloxycarbonylphenyl 2,6-dibenzyloxy-4-benzyloxycarbonylphenyl ketone 9**

To a stirred solution of **8** (0.4 g, 1.26 mmol) in dry DMF (30 cm$^3$) at 0 °C NaH (60% in oil; 0.3 g, 7.56 mmol) was added portionwise and the mixture was allowed to warm to room temperature with stirring for 1 h. After treatment with benzyl bromide (0.9 cm$^3$, 7.57 mmol), the mixture was heated at 65 °C for 20 h. The mixture was cooled to 0 °C and treated with a further quantity of NaH (0.15 g, 3.78 mmol) after which it was stirred at room temperature for 30 min, and then treated with benzyl bromide (0.9 cm$^3$, 7.57 mmol). After being heated at 65 °C for a further 4 h, the mixture was cooled to 0 °C and

treated with methanol (10 $cm^3$); it was then evaporated under reduced pressure. The residue was treated with water (60 $cm^3$) and then extracted with ethyl acetate (3 × 50 $cm^3$). The combined extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was chromatographed on a Dynamax silica column (20 mm × 300 mm) eluting with heptane–ethyl acetate (85:15, v/v) to yield **9** (0.4 g, 42%) as a white solid, mp 127–130 °C (Found C, 77.9; H, 5.1. $C_{50}H_{40}O_8$ requires C, 78.1; H, 5.2%); $\nu_{max}$(KBr)/$cm^{-1}$ 1720s and 1680s (CO); $\delta_H$($CDCl_3$) 4.70 (2 H, s, 6-OC$H_2$Ph), 4.78 (4 H, s, 2'- and 6'-OC$H_2$Ph), 5.12 (2 H, s, 2-$CO_2$C$H_2$Ph), 5.38 (2 H, s, 4'-$CO_2$C$H_2$Ph), 6.82 (2 H, m), 6.95 (1 H, d, *J* 8) and 7.01–7.48 (27 H, m); *m/z* 769 ($MH^+$).

**2-Benzyloxy-6-benzyloxycarbonylphenyl 2,6-dibenzyloxy-4-carboxyphenyl ketone 10**

To a stirred mixture of **9** (0.4 g, 0.52 mmol) in ethanol (30 $cm^3$), a solution of $Na_2CO_3$ (0.24 g, 1.04 mmol) in water (30 $cm^3$), was added and the mixture heated at reflux for 4 h. The mixture was allowed to cool to room temperature after which the ethanol was removed under reduced pressure. Water (150 $cm^3$) was added to the residue and the solution adjusted to pH 1 by the addition of concentrated aq. HCl. The aqueous mixture was then extracted with ethyl acetate (3 × 50 $cm^3$) and the combined extracts were dried ($MgSO_4$), filtered and the solvent was evaporated under reduced pressure to yield a pale yellow solid. Trituration of this with diethyl ether gave **10** (320 mg, 91%) as a white solid, mp 132–134 °C; $\delta_H$($CDCl_3$) 4.72 (2 H, s, 6-OC$H_2$Ph), 4.80 (4 H, s, 2'- and 6'-OC$H_2$Ph), 5.14 (2 H, s, 2'-$CO_2$C$H_2$Ph), 6.85 (2 H, d, *J* 8), 6.97 (1 H, d, *J* 8), 7.05–7.08 (4 H, m), 7.13 (2 H, t, *J* 8, 4-H) and 7.18–7.34 (16 H, m); *m/z* 679 ($MH^+$). Spectroscopic data of **10** were identical with those reported.[7d,8]

**3-Bromo-1-(4'-methylphenylsulfonyl)piperidin-4-one 11**

To a solution of 1-(4'-methylphenylsulfonyl)piperidin-4-one (262.2 g, 1.036 mol) in dichloromethane (6.5 $dm^3$) at −5 °C, a solution of bromine (51.8 $cm^3$, 1.004 mol) in dichloromethane (1 $dm^3$) was added dropwise during 2 h. The temperature of the mixture was maintained between −4 and −2 °C during the first 90 min of the addition and allowed to rise to 0 °C during the last 30 min. The resulting solution was allowed to warm to room temperature with stirring over 1 h. Saturated aq. $NaHCO_3$ (2 $dm^3$) was added to the reaction mixture followed by water (2 $dm^3$) and the resulting biphasic system was stirred for 30 min; the layers were then separated. The organic phase was extracted with aq. $NaHCO_3$ (2.5 $dm^3$) and then dried, ($MgSO_4$), filtered and evaporated under reduced pressure to give **11** (340 g, 98%) as a white solid, mp 129–134 °C (Found: C, 43.2; H, 4.2; N, 4.3. $C_{12}H_{14}BrNO_3S$ requires C, 43.4; H, 4.25; N, 4.2%); $\nu_{max}$(KBr)/$cm^{-1}$ 1735s (CO), 1340s and 1160s ($SO_2$); $\delta_H$($CDCl_3$) 2.45 (3 H, s, 4'-Me), 2.66 (1 H, dddd, *J* 14.8, 8.9, 5.7 and 1.2, 5-$H_{ax}$), 2.96 (1 H, ddd, *J* 14.8, 5.7 and 4.5, 5-$H_{eq}$), 3.25 (1 H, dddd, *J* 12.4, 8.9, 4.5 and 1.2, 6-$H_{ax}$), 3.36 (1 H, ddd, *J* 12.8, 8.4 and 1.2, 2-$H_{ax}$), 3.65 (1 H, dtd, *J* 12.4, 5.7 and 1.8, 6-$H_{eq}$), 3.98 (1 H, ddd, *J* 12.8, 5.1 and 1.8, 2-$H_{eq}$), 4.55 (1 H, ddd, *J* 8.4, 5.1 and 1.2, 3-H), 7.36 (2 H, d, *J* 8, 3'- and 5'-H) and 7.7 (2 H, d, *J* 8, 2'- and 6'-H); *m/z* 331 and 333 ($M^+$).

**3-Bromo-5-ethoxycarbonyl-1-(4'-methylphenylsulfonyl)azepan-4-one 12**

To a solution of **11** (25.1 g, 75.6 mmol) in dichloromethane (822 $cm^3$) at −5 °C under nitrogen, a solution of boron trifluoride–diethyl ether (9.96 $cm^3$, 79.3 mmol) in dichloromethane (117 $cm^3$) was added dropwise over 15 min, the temperature of the mixture being kept between −5 and −3 °C. The solution was stirred at −5 °C for 20 min after which a solution of ethyl diazoacetate (9.93 $cm^3$, 94.4 mmol) in dichloromethane (117 $cm^3$) was added dropwise to it during 20 min, the temperature of the solution being maintained between −5 and −2 °C during the addition. The solution was allowed to warm to room temperature for 90 min, after which it was diluted with water (234 $cm^3$) and then stirred at room temperature for 25 min. The layers were separated and the organic layer was dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to give a pale yellow oily solid which was crystallised from ethyl acetate to yield **12** (22.4 g, 71%) as a colourless solid, mp 165–167 °C (Found: C, 45.6; H, 4.75; N, 3.2. $C_{16}H_{20}BrNO_5S$ requires C, 45.9; H, 4.8; N, 3.3%); $\nu_{max}$(KBr)/$cm^{-1}$ 1740s and 1710s (CO), 1340s and 1160s ($SO_2$); $\delta_H$($CDCl_3$) 1.26 (3 H, t, $CH_3CH_2O$), 2.05 (1 H, dtd, *J* 14.7, 12.1 and 4.9, 6-$H_b$), 2.20 (1 H, dq, *J* 14.7 and 2.9, 6-$H_a$), 2.45 (3 H, s, 4'-Me), 2.81 (1 H, ddd, *J* 14.0, 12.1 and 2.9, 7-$H_b$), 3.07 (1 H, dd, *J* 15.3 and 11.0, 2-$H_b$), 4.00 (1 H, dddd, *J* 14.0, 4.9, 2.9 and 0.9, 7-$H_a$), 4.02 (1 H, dd, *J* 12.1 and 2.9, 5-$H_a$), 4.19 (2 H, q, $CH_3CH_2O$), 4.27 (1 H, m, *J* 15.3, 6.5 and 0.9, 2-$H_a$), 4.45 (1 H, dd, *J* 11.0 and 6.5, 3-H), 7.34 (2 H, d, *J* 8, 3'- and 5'-H) and 7.67 (2 H, d, *J* 8, 2'-and 6'-H); *m/z* 418 and 420 ($MH^+$).

**3-Bromo-1-(4'-methylphenylsulfonyl)azepan-4-one 13**

To a suspension of **12** (45.4 g, 0.109 mol) in 1,4-dioxane (680 $cm^3$) at 80 °C aq. HCl (3 mol $dm^{-3}$; 364 $cm^3$) was added during 10 min. The resulting solution was heated at reflux for 7 h, cooled to room temperature and kept for 16 h. After this it was evaporated under reduced pressure to give a pale brown solid which was dissolved in ethyl acetate (650 $cm^3$) and the solution washed with water (2 × 50 $cm^3$) and brine (50 $cm^3$) dried ($Na_2SO_4$), filtered, and evaporated under reduced pressure to afford a pale brown crystalline solid. This was recrystallised from diisopropyl ether to give **13** (33.9 g, 90%) as a colourless crystalline solid, mp 104–106 °C (Found: C, 45.2; H, 4.7; N, 4.0 $C_{13}H_{16}BrNO_3S$ requires C, 45.1; H, 4.7; N, 4.05%); $\nu_{max}$(KBr)/$cm^{-1}$ 1710s (CO), 1340s and 1160s ($SO_2$); $\delta_H$($CDCl_3$) 1.87 (1 H, m, 6-$H_b$), 1.96 (1 H, m, 6-$H_a$), 2.45 (3 H, s, 4'-Me), 2.56 (1 H, ddd, *J* 12.4, 6.8 and 2.6, 5-$H_b$), 2.77 (1 H, ddd, *J* 13.7, 11.7 and 3.4, 7-$H_b$), 2.88 (1 H, td, *J* 12.4 and 3.4, 5-$H_a$), 3.05 (1 H, dd, *J* 15.1 and 11.0, 2-$H_b$), 4.0 (1 H, dt, *J* 13.7 and 3.8, 7-$H_a$), 4.24 (1 H, ddd, *J* 15.1, 6.4 and 1.10, 2-$H_a$), 4.38 (1 H, dd, *J* 11.0 and 6.4, 3-H), 7.34 (2 H, d, *J* 8, 3'- and 5'-H) and 7.67 (2 H, d, *J* 8, 2'- and 6'-H); *m/z* 346 and 348 ($MH^+$).

**3-Azido-1-(4'-methylphenylsulfonyl)azepan-4-one 14**

To a solution of **13** (33.9 g, 97.9 mmol) in dry DMF (750 $cm^3$) under argon, acetic acid (11.2 $cm^3$) and then sodium azide (12.7 g, 0.195 mol) were added. The resulting suspension was stirred at room temperature for 3.5 h and then kept at room temperature for 16 h. Upon dilution of the mixture with water (1.875 $dm^3$) an oily solid separated and this was extracted with ethyl acetate (1 × 900 $cm^3$, 3 × 300 $cm^3$). The combined extracts were washed with brine (225 $cm^3$) dried ($Na_2SO_4$), filtered and evaporated under reduced pressure to yield a yellow viscous liquid which crystallised when kept at room temperature. Recrystallisation of this from *tert*-butyl methyl ether gave **14** (21.9 g, 73%) as a white crystalline solid, mp 88 °C (Found: C, 50.3; H, 5.15; N, 17.8. $C_{13}H_{16}N_4O_3S$ requires C, 50.6; H, 5.2; N, 18.1%); $\nu_{max}$(KBr)/$cm^{-1}$ 2090s ($N_3$), 1710s (CO), 1340s and 1160s ($SO_2$); $\delta_H$($CDCl_3$) 1.89 (1 H, dddd, *J* 14.8, 8.2, 6.5 and 4.2, 6-$H_b$), 1.95 (1 H, m, 6-$H_a$), 2.45 (3 H, s, 4'-Me), 2.64 (1 H, ddd, *J* 13.8, 9 and 4.2, 5-$H_b$), 2.69 (1 H, ddd, *J* 13.8, 8.2 and 4.2, 5-$H_a$) 3.02 (1 H, ddd, *J* 13.7, 8.2 and 4.2, 7-$H_b$), 3.04 (1 H, dd, *J* 14.8 and 8.7, 2-$H_b$), 3.68 (1 H, dddd, *J* 13.7, 6.5, 4.2 and 1, 7-$H_a$), 3.78 (1 H, ddd, *J* 14.8, 5.3 and 1, 2-$H_a$), 4.21 (1 H, dd, *J* 8.7 and 5.3), 7.34 (2 H, d, *J* 8, 3'- and 5'-H) and 7.68 (2 H, d, *J* 8, 2'- and 6'-H).

***trans*-3-Azido-1-(4'-methylphenylsulfonyl)azepan-4-ol 15 and *cis*-3-azido-1-(4'-methylphenylsulfonyl)azepan-4-ol 16**

To a suspension of **14** (21.8 g, 70.7 mmol) in ethanol (220 $cm^3$)

at 0 °C sodium boranuide (2.67 g, 70.06 mmol) was added portionwise over 10 min. The resulting clear solution was stirred at 2–5 °C for 15 min after which it was cooled in an ice–water bath whilst water (670 $cm^3$) was added to it followed by aq. HCl (1 mol $dm^{-3}$; 110 $cm^3$), added dropwise over 10 min as the mixture was allowed to warm to *ca.* 20 °C. The mixture was then stirred at *ca.* 20 °C for 15 min after which it was further diluted with water (440 $cm^3$) to give separation of a yellow oil which was extracted with ethyl acetate (1 × 440 $cm^3$, 3 × 220 $cm^3$). The combined extracts were washed with brine (2 × 55 $cm^3$), dried ($Na_2SO_4$), filtered and evaporated under reduced pressure. The products were purified on $SiO_2$ eluting with *tert*-butyl methyl ether–pentane (1:1, v/v to 7:3, v/v): to give **16** (13.5 g, 62%) as a white solid, mp 87–90 °C (Found: C, 50.15; H, 5.75; N, 18.15. $C_{13}H_{18}N_4O_3S$ requires C, 50.31; H, 5.85; N, 18.05%); $\nu_{max}$(KBr)/$cm^{-1}$ 3510br (OH), 2940s ($N_3$), 1340s and 1160s ($SO_2$); $\delta_H$($CDCl_3$) 1.73 (2 H, m, 6-H), 1.98 (2 H, m, 5-H), 2.05 (1 H, dd, *J* 3.6 and 1.2, -OH), 2.45 (3 H, s, 4′-Me), 2.93 (1 H, dt, *J* 12.4 and 5.9, 7-$H_b$), 3.08 (1 H, dd, *J* 14.4 and 9.6, 2-$H_b$), 3.61 (2 H, m, 2-$H_a$ and 7-$H_a$), 3.78 (1 H, ddd, *J* 9.6, 3.9 and 3.3, 3-H), 4.1 (1 H, br m, 4-H), 7.34 (2 H, d, *J* 8, 3′- and 5′-H) and 7.68 (2 H, d, *J* 8, 2′- and 6′-H); and **15** (5.7 g, 26%) as a white solid, mp 67–70 °C (Found: C, 50.2; H, 5.8; N, 18.1. $C_{13}H_{18}N_4O_3S$ requires C, 50.3; H, 5.85; N, 18.05%); $\nu_{max}$(KBr)/$cm^{-1}$ 3510br (OH), 2940s ($N_3$), 1340s and 1160s ($SO_2$); $\delta_H$($CDCl_3$) 1.54 (1 H, m, 6-$H_b$), 1.78 (1 H, m, 6-$H_a$), 1.96 (2 H, m, 5-H), 2.22 (1 H, d, *J* 3.9, OH), 2.45 (3 H, s, 4′-Me), 2.82 (1 H, dd, *J* 14.8 and 9, 2-$H_b$), 3.01 (1 H, ddd, *J* 12.2, 6.5 and 3.5, 7-$H_b$), 3.48 (2 H, m, 4-H and 7-$H_a$), 3.53 (1 H, dd, *J* 9 and 3.6, 3-H), 3.66 (1 H, ddd, *J* 14.8, 3.6 and 0.9, 2-$H_a$), 7.34 (2 H, d, *J* 8, 3′- and 5′-H) and 7.68 (2 H, d, *J* 8, 2′- and 6′-H).

***trans*-3-Azido-1-(4′-methylphenylsulfonyl)-4-(4″-nitrobenzoyloxy)azepane 17**

To a solution of triphenylphosphine (17.6 g, 67.1 mmol) in dry THF (330 $cm^3$) at 5 °C, DIAD (diisopropylazodicarboxylate; 13.9 $cm^3$, 67.1 mmol) was added dropwise during 10 min while the temperature of the mixture was kept at 5–10 °C. A thick cream suspension formed which was stirred for a further 15 min and to this 4-nitrobenzoic acid (11.2 g, 67 mmol) and **16** (13.4 g, 43.2 mmol) were added. The resulting yellow solution was allowed to warm to room temperature as it was stirred for 1 h and then kept at room temperature for 16 h. After this the mixture was evaporated under reduced pressure and the residue stirred with *tert*-butyl methyl ether (170 $cm^3$) to yield a cream solid. The product was crystallised from *tert*-butyl methyl ether to give **17** (16.9 g, 85%) as colourless crystals, mp 164–168 °C (Found: C, 52.3; H, 4.6; N, 15.1. $C_{20}H_{21}N_5O_6S$ requires C, 52.3; H, 4.6; N, 15.2%); $\nu_{max}$(KBr)/$cm^{-1}$ 2105s ($N_3$), 1720s (CO), 1530s and 1350w ($NO_2$), 1330s and 1160s ($SO_2$); $\delta_H$($CDCl_3$) 1.70 (1 H, m, 6-$H_b$), 2.06 (3 H, m, 5-H and 6-$H_a$), 2.45 (3 H, s, 4′-Me), 2.82 (1 H, dd, *J* 15 and 10, 2-$H_b$), 2.97 (1 H, ddd, *J* 12.3, 6.6 and 3.5, 7-$H_b$), 3.64 (1 H, ddd, *J* 12.3, 9.8 and 6.6, 7-$H_a$), 3.76 (1 H, ddd, *J* 15, 4.2 and 1, 2-$H_a$), 4.02 (1 H, ddd, *J* 10, 8.4 and 4.2, 3-H), 5.0 (1 H, ddd, *J* 10, 8.4 and 2.9, 4-H), 7.34 (2 H, d, *J* 8, 3′- and 5′-H), 7.7 (2 H, d, *J* 8, 2′- and 6′-H), 8.25 (2 H, d, *J* 8, 3″- and 5″-H) and 8.33 (2 H, d, *J* 8, 2″- and 6″-H).

**Conversion of *trans*-3-azido-1-(4′-methylphenylsulfonyl)-4-(4″-nitrobenzoyloxy)azepane 17 into *trans*-3-azido-1-(4′-methylphenylsulfonyl)azepan-4-ol 15**

To a suspension of **17** (16.9 g, 36.8 mmol) in methanol (750 $cm^3$) and 1,4-dioxane (190 $cm^3$) was added aq. NaOH (2% w/v; 150 $cm^3$) at room temperature. The suspension was stirred at room temperature for 5 h; a clear solution was obtained after 3 h. The solution was kept at room temperature for 16 h, after which it was evaporated under reduced pressure to give an oily residue which was stirred with ethyl acetate (460 $cm^3$) and water (460 $cm^3$). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 230 $cm^3$). The combined organic layer and extracts were washed with brine (2 × 50 $cm^3$), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to give a viscous liquid, which crystallised with time to give **15** (11.3 g, 99%) mp 66–70 °C, identical with **15** as prepared above.

***trans*-3-Amino-1-(4′-methylphenylsulfonyl)azepan-4-ol 18**

To a solution of **15** (16.9 g, 54.5 mmol) in dry THF (270 $cm^3$) at 0 °C under nitrogen, a solution of lithium aluminium hydride in THF (1 mol $dm^{-3}$; 27.3 $cm^3$, 27.3 mmol) was added dropwise during 10 min, while the temperature of the mixture was kept at 0–2 °C. After the mixture had been allowed to warm to room temperature it was stirred for 45 min. Water (30 $cm^3$) was then added dropwise during 10 min to the mixture with cooling (ice–water bath) followed by aq. $Na_2CO_3$ (275 $cm^3$; 20% w/v). The mixture was diluted with water (2 $dm^3$) and extracted with ethyl acetate (1 × 1 $dm^3$, 3 × 450 $cm^3$) and the combined extracts were washed with brine (2 × 150 $cm^3$), dried ($Na_2SO_4$), filtered and evaporated under reduced pressure to give a colourless oil which crystallised with time. The product was recrystallised from *tert*-butyl methyl ether to give **18** (13.1 g, 85%) as colourless crystals, mp 93–96 °C (Found: C, 54.8; H, 7.05; N, 9.6. $C_{13}H_{20}N_2O_3S$ requires C, 54.9; H, 7.1; N, 9.85%); $\nu_{max}$(KBr)/$cm^{-1}$ 3360br (OH), 3100br and 2930br ($NH_2$), 1330s and 1150s ($SO_2$); $\delta_H$($CDCl_3$) 1.64 (2 H, m, 6-H), 1.94 (2 H, m, 5-H), 2.45 (3 H, s, 4′-Me), 2.76 (1 H, td, *J* 8.1, 8.1 and 3.5, 3-H), 2.86 (1 H, dd, *J* 14.2 and 8.1, 2-$H_b$), 3.18 (1 H, ddd, *J* 12.6, 6.1 and 4.4, 7-$H_b$), 3.22 (1 H, m, 7-$H_a$), 3.29 (1 H, ddd, *J* 9.8, 8.1 and 2.4, 4-H), 3.49 (1 H, ddd, *J* 14.2, 3.5 and 0.6, 2-$H_a$), 7.31 (2 H, d, *J* 8, 3′- and 5′-H) and 7.66 (2 H, d, *J* 8, 2′- and 6′-H); *m/z* 285 ($MH^+$).

***trans*-3-Aminoazepan-4-ol dihydrobromide 19**

A suspension of **18** (13.0 g, 45.7 mmol) in aq. HBr (48%; 130 $cm^3$) was stirred and heated to reflux at which temperature the resulting yellow solution was kept for 3 h. The solution was then cooled to room temperature and kept for 16 h after which it was diluted with ice–water (260 $cm^3$) and then extracted with *tert*-butyl methyl ether (1 × 160 $cm^3$, 2 × 40 $cm^3$). The aqueous layer was concentrated under reduced pressure to give an oily yellow solid which was crystallised from ethanol to yield **19** (9.09 g, 68%) as a white crystalline solid, mp 215 °C (decomp.) (Found: C, 24.5; H, 5.6; N, 9.4. $C_6H_{16}Br_2N_2O$ requires C, 24.7; H, 5.5; N, 9.4%); $\nu_{max}$(KBr)/$cm^{-1}$ 3420br, 3230br and 2900br; $\delta_H$($CD_3SOCD_3$) 1.6–1.65 (3 H, m), 1.79–1.81 (1 H, m), 1.95–2.05 (1 H, m), 3.05–3.2 (3 H, m), 3.65 (1 H, br), 5.75 (1 H, br), 8.18 (3 H, br) and 9.1 (1 H, br).

***trans*-3-Amino-1-benzyloxycarbonylazepan-4-ol 20**

To a stirred suspension of **19** (9.01 g, 30.9 mmol) in dry dichloromethane (230 $cm^3$) at room temperature under nitrogen, triethylamine (21.5 $cm^3$) was added followed by 18-crown-6 (16.3 g, 61.7 mmol). The mixture was stirred at room temperature for 20 min and the resulting clear solution cooled to 5 °C and benzyl chloroformate (4.97 $cm^3$, 33.9 mmol) was added dropwise during 10 min. The mixture was stirred at room temperature for 5 h, allowed to stand at room temperature for 16 h and then concentrated under reduced pressure to give a pale yellow oily solid which was stirred with ethyl acetate (330 $cm^3$) and aq. $Na_2CO_3$ (10% w/v; 220 $cm^3$). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 110 $cm^3$). The combined organic extracts were washed with aq. $Na_2CO_3$ (10% w/v 110 $cm^3$) and saturated aq. KBr (2 × 55 $cm^3$), dried ($Na_2SO_4$), filtered and the mixture was concentrated under reduced pressure to give a pale yellow oily solid. Crystallisation from *tert*-butyl methyl ether gave **20**

(7.19 g, 88%) as a colourless crystalline solid, mp 78–80 °C (Found: C, 63.7; H, 7.8; N, 10.7. $C_{14}H_{20}N_2O_3$ requires C, 63.6; H, 7.6; N, 10.6%); $\nu_{max}$(KBr)/cm$^{-1}$ 3350br, 3270br and 2900br, 1700s (CO); $\delta_H$($CDCl_3$) 1.48 (1 H, m, 6-$H_b$), 1.61 (1 H, m, 6-$H_a$) 1.96 (2 H, m, 5-H), 2.66 (½ H, dt, *J* 9,9 and 3.7, 3-H), 2.70 (½ H, dt, *J* 9,9 and 3.7, 3-H), 2.87 (½ H, dd, *J* 14.4 and 9, 2-$H_b$), 2.97 (½ H, dd, *J* 14.4 and 9, 2-$H_b$), 3.22 (1½ H, m, 7-$H_b$ and 4-H), 3.33 (½ H, ddd, *J* 13.6, 5.9 and 4.3, 7-$H_b$), 3.53 (½ H, ddd, *J* 13.6, 9.9 and 5.9, 7-Ha), 3.66 (½ H, ddd, *J* 13.6, 9.9 and 5.9, 7-Ha), 3.71 (½ H, dd, *J* 14.5 and 3.8, 2-$H_a$), 3.79 (½ H, dd, *J* 14.5 and 3.8, 2-$H_a$), 5.12, 5.17 (AB system, 2 H, *J* 12, PhC$H_2$) and 7.28–7.4 (5 H, m, Ar); *m/z* 265 ($MH^+$).

***trans*-3-[4-(Benzyloxy)benzamido]-1-benzyloxycarbonylazepan-4-ol 21**

To a stirred suspension of **20** (3.09 g, 11 mmol) in dichloromethane (60 cm$^3$) at 0 °C, triethylamine (2.28 cm$^3$, 16.4 mmol) was added. While the temperature of the mixture was maintained at *ca.* 0 °C, 4-(benzyloxy)benzoyl chloride (3.02 g, 11 mmol) in dichloromethane (30 cm$^3$) was added dropwise after which the mixture was stirred at *ca.* 0 °C for a further 3 h. The mixture was then evaporated under reduced pressure and the residue dissolved in ethyl acetate (500 cm$^3$). The resulting solution was washed with water (2 × 60 cm$^3$) and brine (1 × 60 cm$^3$), dried ($Na_2SO_4$), filtered and evaporated under reduced pressure to yield a viscous yellow oil. Chromatography of the oil on silica, eluting with *tert*-butyl methyl ether gave a colourless viscous oil, crystallisation of which from diisopropyl ether gave **21** (3.29 g, 63%) as a colourless solid, mp 132–134 °C (Found: C, 70.8; H, 6.4; N, 5.8. $C_{28}H_{30}N_2O_5$ requires C, 70.9; H, 6.4; N, 5.9%); $\nu_{max}$(KBr)/cm$^{-1}$ 3330br (OH), 2950br (NH) and 1700s (CO); $\delta_H$($CDCl_3$) 1.66 (1 H, m, 6-$H_b$), 1.78–2.0 (3 H, m, 5- and 6-$H_a$), 2.78 (1 H, ddd, *J* 14, 13 and 4, 7-$H_b$), 3.35 (1 H, dd, *J* 15 and 5, 2-$H_b$), 3.78 (1 H, ddd, *J* 10, 6 and 2, 4-H), 4.07–4.23 (3 H, m, 2-$H_a$, 3-H and 7-$H_a$), 5.12 (2 H, s, OC$H_2$Ph), 5.14, 5.21 (AB system, 2 H, *J* 12, PhC$H_2$), 5.46 (1 H, br, s, OH), 7.02 (2 H, d, *J* 8, Ar), 7.28–7.47 (10 H, m, Ar), 7.82 (2 H, d, *J* 8, Ar) and 8.83 (1 H, br d, NH); *m/z* 475 ($MH^+$). Spectroscopic data of **21** were identical with those reported.[8]

**Separation of the enantiomers of 21**

To a solution of **21** (170 mg, 0.36 mmol), triethylamine (0.1 cm$^3$, 0.72 mmol) and DMAP (4-dimethylaminopyridine; 44 mg, 0.36 mmol) in dichloromethane (5 cm$^3$), the acid chloride derived from (*S*)-(-)-MTPA [α-methoxy-α-(trifluoromethyl)phenylacetic acid; 113 mg, 0.45 mmol] in dichloromethane (2 cm$^3$) was added dropwise at room temperature. The mixture was stirred at room temperature for 16 h after which it was evaporated under reduced pressure. The residue was chromatographed on silica eluting with ethyl acetate–pentane (1:3, v/v) to give the enantiomerically pure Mosher's esters **22a** (120 mg, 48%); *m/z* 691 ($MH^+$), and **22b** (120 mg, 48%); *m/z*; 691 ($MH^+$). Both **22a** and **22b** appear as a *ca.* 3:1 rotameric mixture by $^1$H NMR. Separate solutions of both **22a** (120 mg, 0.17 mmol) and **22b** (120 mg, 0.17 mmol) in methanol (5 cm$^3$) were stirred and treated with aq. KOH (1 mol dm$^{-3}$; 2 cm$^3$). Each reaction mixture was stirred at room temperature for 16 h and then diluted with diethyl ether (30 cm$^3$) and water (20 cm$^3$). The organic layer was separated and evaporated under reduced pressure to yield a colourless gum, treatment of which with diisopropyl ether gave, as white solids, **21a** (80 mg, 100%), mp 113–114 °C, and **21b** (80 mg, 100%), mp 116–118 °C. Both **21a** and **21b** were identical spectroscopically with **21**. The enantiomeric purity of **21a** and **21b** was assessed relative to racemic **21** using chiral chromatography on a Chiral Pack AD column (4.6 mm × 250 mm) eluting with ethanol–heptane (15:85, v/v) which showed **21a** and **21b** both to be >99% enantiomerically pure.

**Protected balanol 23**

To a stirred solution of **10** (180 mg, 0.265 mmol), triethylamine (0.74 cm$^3$, 5.3 mmol) and DMAP (16.4 mg, 0.133 mmol) in dichloromethane (9 cm$^3$), 2-chloro-1-methylpyridinium iodide (88 mg, 0.345 mmol) was added and the mixture stirred at room temperature for 1 h. Compound **21** (125 mg, 0.26 mmol) was added to the mixture which was then, stirred at room temperature for 20 h and finally heated at reflux for 2 h. After being cooled to room temperature the mixture was evaporated under reduced pressure and the residue dissolved in ethyl acetate (20 cm$^3$). The resulting solution was washed with aq. $NaHCO_3$ (5%; 2 × 50 cm$^3$), dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification of the residue on silica eluting with ethyl acetate–dichloromethane (5:95, v/v) gave **23** (0.11 g, 37%) as a glass; *m/z* 1135 ($MH^+$); $\delta_H$($CDCl_3$) as a *ca.* 3:1 rotameric mixture 1.6–2.1 (4 H, m), 2.9 (1 H, m), 3.4 (1 H, m), 4.08–4.16 (2 H, m), 4.67 (2 H, s, OC$H_2$Ph), 4.7–4.88 (1 H, m), 4.82, 4.85 (2 H, AB system, *J* 12, OC$H_2$Ph), 5–5.15 (1 H, m), 5.04 (2 H, s, OC$H_2$Ph), 5.1 (4 H, s, OC$H_2$Ph), 5.26 (2 H, s, OC$H_2$Ph), 6.82 (2 H, d, *J* 8, Ar), 6.88–6.95 (4 H, m, Ar), 7.0–7.45 (32 H, m, Ar), 7.72 and 7.79 (*ca.* 3:1, 2 H, d, *J* 8, Ar). Spectroscopic data were identical with those reported;[8] the presence of rotamers precludes the exact assignment of all resonances.

**Balanol 1**

A solution of **23** (106 mg, 0.093 mmol) in ethyl acetate–acetic acid–water (19 cm$^3$, 16:2:1, v/v) was treated with palladium black (10.6 mg) under an atmosphere of hydrogen. The reaction mixture was initially warmed to 50 °C and then stirred at room temperature for 4 h. After this the mixture was filtered and fresh catalyst (10.6 mg) added, to the filtrate; the reaction mixture was then placed under a fresh atmosphere of hydrogen and stirred at room temperature for 24 h. The catalyst was filtered off and washed with a solvent mixture (16 cm$^3$) as used for the reaction. The mixture was concentrated and the residue was chromatographed on a Dynamax $C_{18}$ column (20 × 300 mm) eluting with acetonitrile–water–trifluoroacetic acid (20:80:0.1, v/v) to give **1** (27 mg, 53%) as a light yellow powder; *m/z* 551 ($MH^+$); $\delta_H$($CD_3OD$) 1.84–2.12 (4 H, br m, 5- and 6-H), 3.42–2.98 (4 H, br m, 2- and 7-H), 4.32 (1 H, br m, 3-H), 5.29 (1 H, m, 4-H), 6.76 (2 H, d, *J* 8.7, 4′- and 6′-H), 6.80 (1 H, d, *J* 7.8, 11″-H), 6.92 (2 H, s, 3″- and 7″-H), 7.17 (1 H, t, *J* 7.8, 12″-H), 7.25 (1 H, d, *J* 7.8, 13″-H) and 7.60 (2 H, d, *J* 8.7, 3′-, 7′-H). Spectroscopic data were identical with those reported.[8]

**X-Ray crystal structure determination of *trans*-3-azido-1-(4′-methylphenylsulfonyl)hexahydroazepan-4-ol 15**

A single crystal of compound **15** (from *tert*-butyl methyl ether, appoximate size 0.18 × 0.28 × 0.16 mm), mounted in a Lindemann tube, was used for X-ray data collection.

**Crystal data.** $C_{13}H_{18}N_4O_3S$, $M$ = 310.37, colourless prisms, orthorhombic, space group $Pn2_1a$, $a$ = 8.7030(9), $b$ = 11.3280(13), $c$ = 15.097(2) Å (by least squares refinement of the setting angles for 250 reflections within $\theta$ = 2.25–27.16 °), $V$ = 1488.4(3) Å$^{-3}$, $Z$ = 4, $D_c$ = 1.385 g cm$^{-3}$, $T$ = 120 K, $\mu$(Mo-K$\alpha$) = 2.33 cm$^{-1}$, $F$(000) = 656.

**Data collection, structure solution and refinement.** Data were collected on a FAST TV Area detector diffractometer following previously described methods.[15] From the ranges scanned, 6059 data were recorded (2.25 < $\theta$ < 27.16 °; index ranges $-10 \leqslant h \leqslant 10$, $-13 \leqslant k \leqslant 9$, $-18 \leqslant l \leqslant 10$) and merged to give 2618 unique [$R$(int) = 0.0532]. The structure was solved by direct methods[16] and refined on $F_o^2$ by full matrix least squares[17] using all unique data corrected for Lorentz and polarisation factors. All non-hydrogen atoms were anisotropic. The hydrogen atoms were inserted in idealised positions with $U_{iso}$ set at 1.5 times $U_{eq}$ of the parent. The weighting scheme

used was $w = 1/[\sigma^2(F_o)^2 + (0.0612P)^2]$, where $P = [\max(F_o)^2 + 2(F_c)^2]/3$; this gave satisfactory agreement analysis. Final $R_1$ (on $F$) and $R_{w2}$ (on $F_o^2$) values were 0.0473 and 0.1067 for all 2616 data and 191 parameters. The corresponding $R$ values were 0.0424 and 0.1008 for 2323 data with $I > 2\sigma(I)$. Sources of scattering factors are given in ref. 17.

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